q-bio 2018

Summer School

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Biological Computation Lab

Models

A model only makes sense in terms of some relation that is preserved.

- A model that makes *predictions* about some system
- A models used to define *computation*
- *Existence proof* models (models demonstrating the possibility of something).
- A model used to *explain* something that already happened.

Models

- `Now it would be very remarkable if any system existing in the real world could be *exactly* represented by any simple model. However, cunningly chosen parsimonious models often do provide remarkably useful approximations.´
- `For such a model there is no need to ask the question "Is the model true?". If "truth" is to be the "whole truth" the answer must be "No". The only question of interest is "Is the model illuminating and useful?"´.

Box, G. E. P. (1979), "Robustness in the strategy of scientific model building", in Launer, R. L.; Wilkinson, G. N., Robustness in Statistics, Academic Press, pp. 201–236.

Models

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- “All models are wrong, some are useful.”

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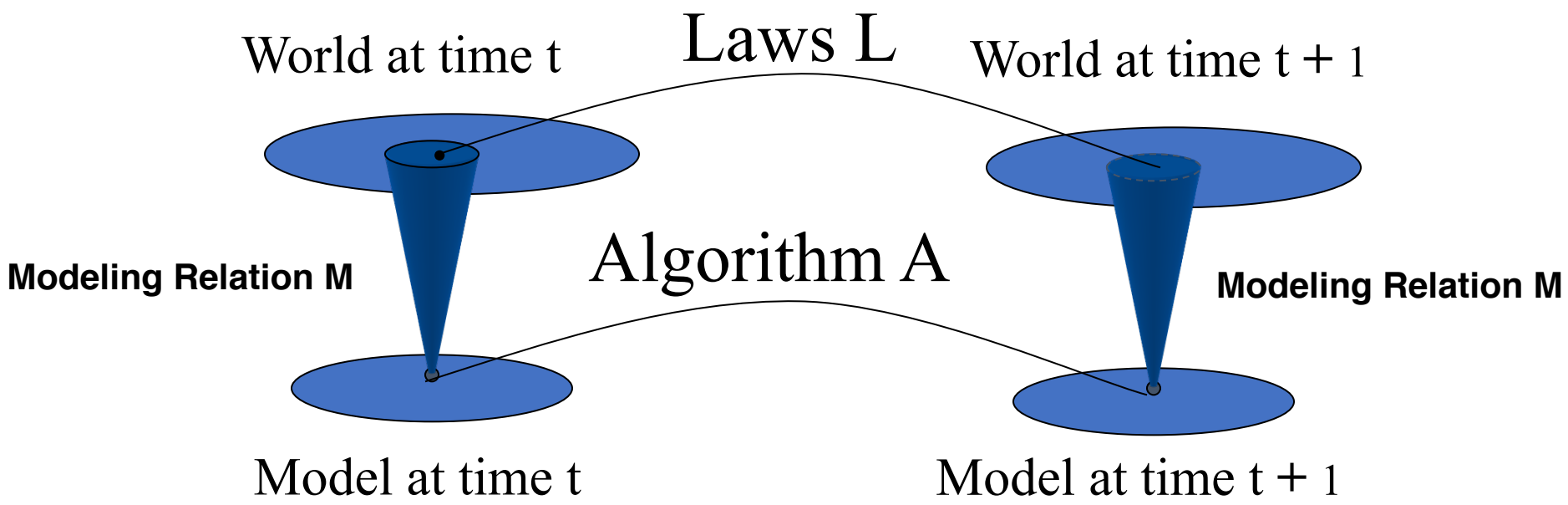
Models as Homomorphic Maps
Commutativity of the Diagram



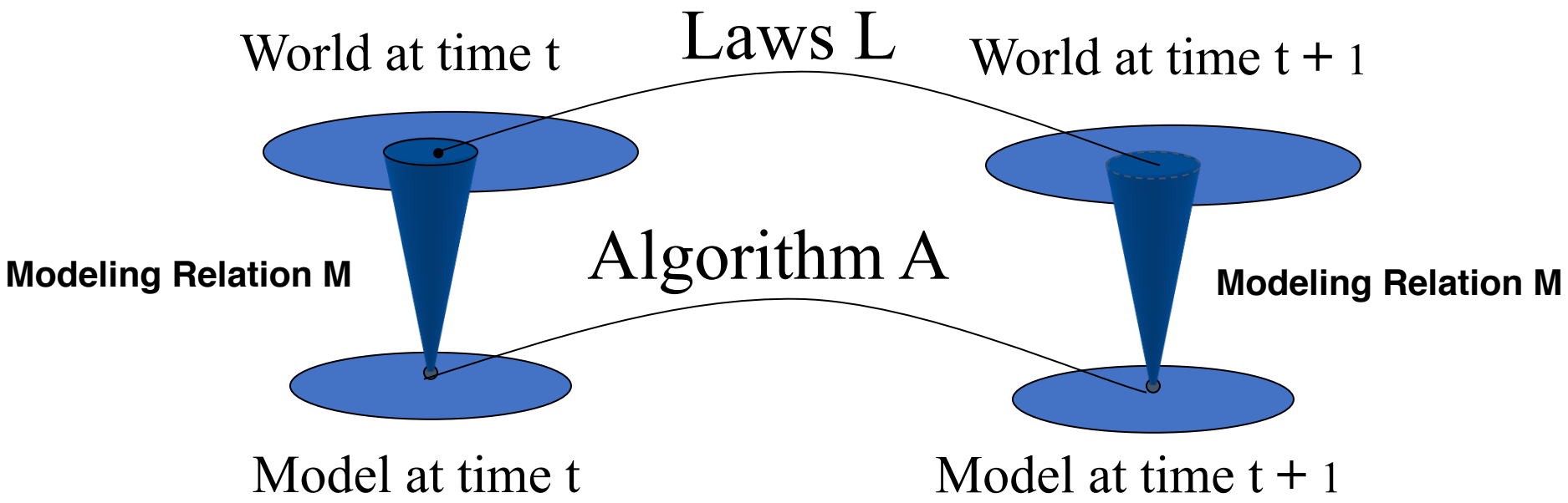
M is an equivalence relation.

Model M is valid if this is a homomorphic map:

$M(L(x)) = A(M(x))$

Models as Homomorphic Maps

transformation of one set into another that preserves in the second set the relations between elements of the first.



Models

- “It can scarcely be denied that the supreme goal of all theory is to make the irreducible basic elements as simple and as few as possible without having to surrender the adequate representation of a single datum of experience.”

Attributed to Albert Einstein in “On the Method of Theoretical Physics,” the Herbert Spencer Lecture, Oxford, June 10, 1933. This is the Oxford University’ Press

Equivalence Classes

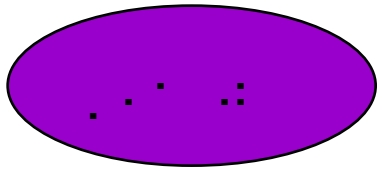
- Equivalence class =

$$\{x \mid x \in R\} \text{ and } R \text{ is an equivalence relation.}$$

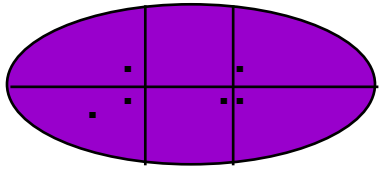
- R is an equivalence relation:
  - Reflexive: $\forall x(xRx)$
  - Symmetric: $xRy \Rightarrow yRx$
  - Transitive: $(xRy) \wedge (yRz) \Rightarrow (xRz)$

The relation does not change unless world changes, the relation is preserved between the model and world, the model and world stay consistent over time.

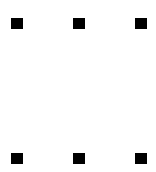
- Example: xRy <=> x and y are in the same little box.



Set of Objects



Partition set into 6 little boxes



Equivalence classes

Examples of Equivalence Relations

- “Is similar to" or "congruent to" on the set of all triangles.
- Logical equivalence of statements in logic.
- "Has the same image under a function" on the elements of the domain of the function.
- What’s not an equivalence relation?
  - The relation "≥" between real numbers is reflexive and transitive, but not symmetric. For example, 7 ≥ 5 does not imply that 5 ≥ 7. It is, however, a partial order.
  - The relation "is a sibling of" on the set of all human beings is not an equivalence relation.
    - Is Symmetric (if A is a sibling of B, then B is a sibling of A)
    - Not reflexive (no one is a sibling of himself),
    - Not transitive (since if A is a sibling of B, then B is a sibling of A, but A is not a sibling of A).

Example Homomorphism:

Multiplication of Integers

- Model all pairs of integers and their product:
  - e.g., 14792 x 4183584 = 61883574528
- Model:
  - Even X Even = Even
  - Even X Odd = Even
  - Odd X Even = Even
  - Odd X Odd = Odd

Example Homomorphism:

Multiplication of Integers

Model:
Even x Even = Even
Even x Odd = Even
Odd x Odd = Odd
Odd x Even = Even

M(L(x)) = M(2n x 2m = 2k) = Even x Even = Even

The relationships are preserved under our model.

Model relationship:

2n x 2m = 2k *R* Even x Even = Even
2n+1 x 2m+1 = 2k+1 *R* Odd x Odd = Odd
2n x 2m+1 = 2k *R* Even x Odd = Even
2n+1 x 2m = 2k+1 *R* Odd x Even = Even

Lattice Gas Models (LGCA)

- Gasses and fluids can be modelled with continuous models
- That is, we can use continuous values of pressure, temperature, and velocity

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  - We have to model the individual molecules of gas.

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- If we are modelling systems with very high energies (such as a nuclear explosion) we have to have a discrete model of the internal states of the atoms involved.

Lattice Gas Models

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- These systems require models of the **microscopic** behaviour

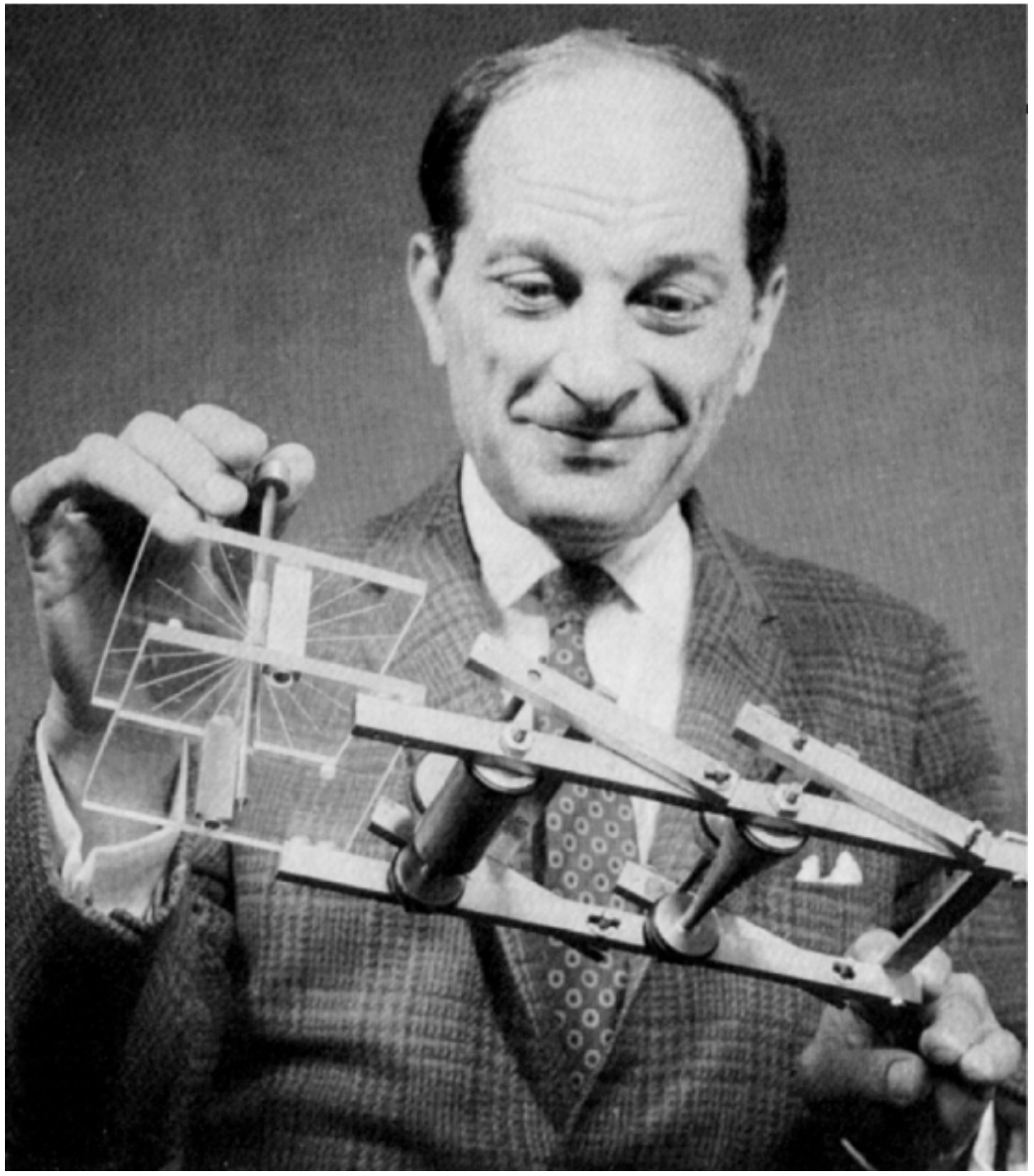
- Models that are able to describe the behaviour of the system using just pressure, velocity, and temperature are **macroscopic**.

- Of course, we could model all gasses and fluids at the microscopic level.

Lattice Gas Models

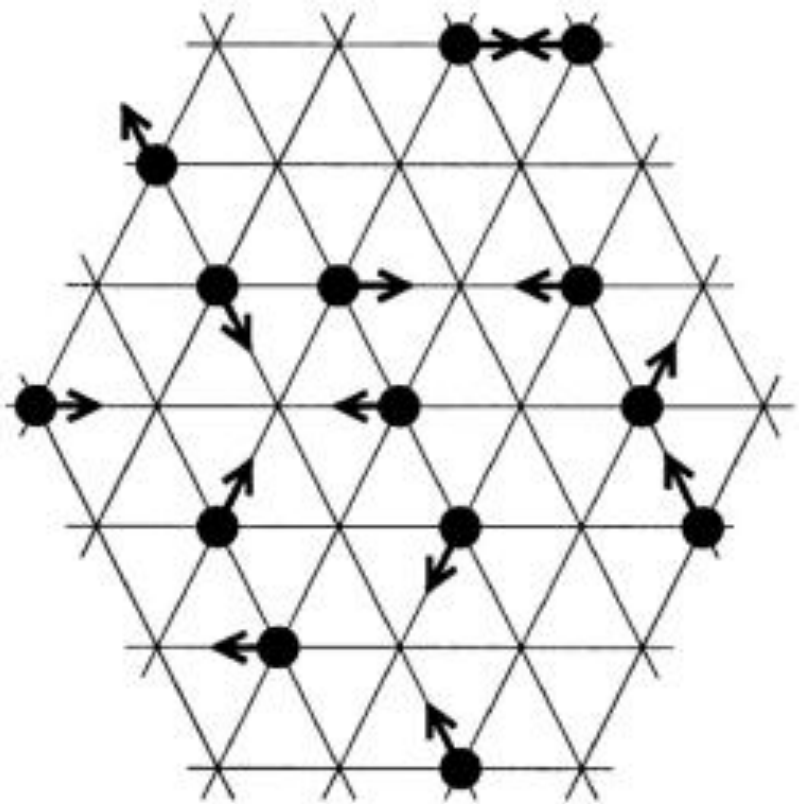
- Cellular automata are used to model molecular systems.

- The use of cellular automata to model particles such as gasses, fluids, and
- The propagation of subatomic particles was pioneered by Stanislaw Ulam and John von Neumann in the 1950s.

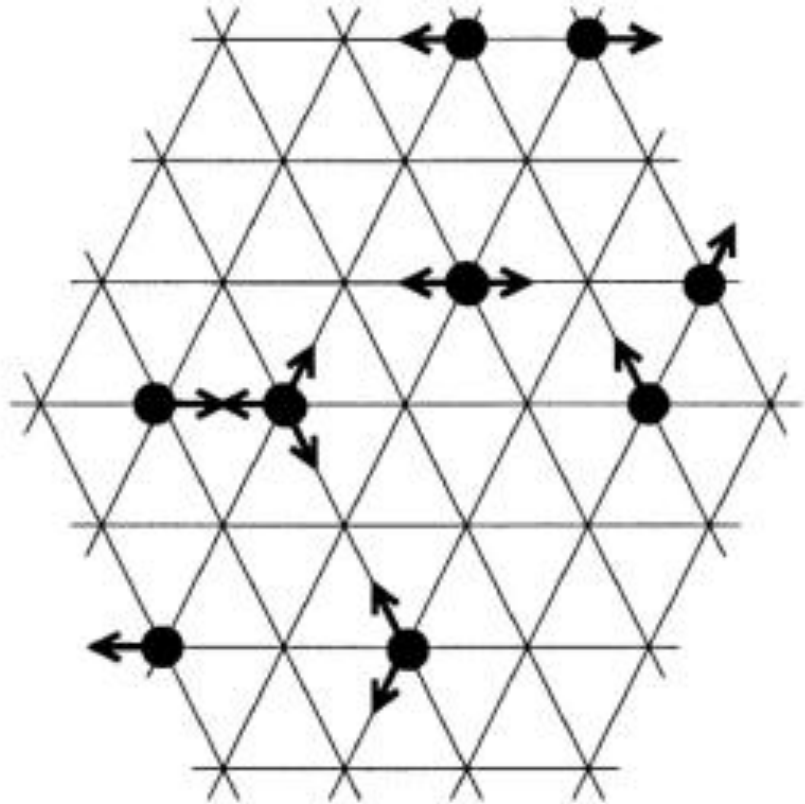


Stanislaw Ulam with the FERMIAC, used to model neutron transport, Los Alamos National Labs

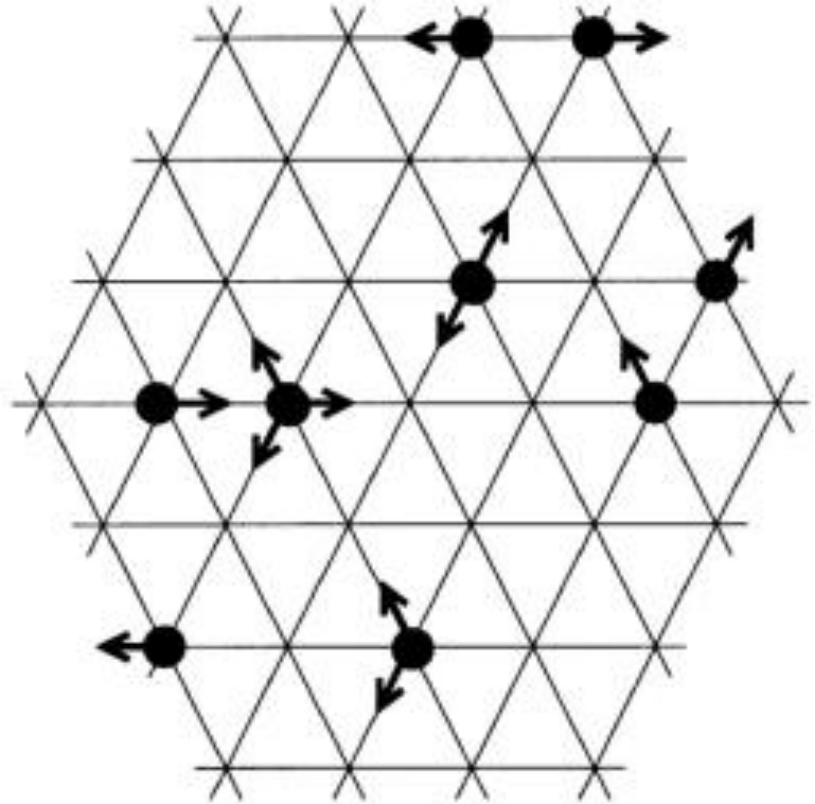
MCNP SOFTWARE QUALITY: THEN AND NOW Gregg C. Giesler, Los Alamos National Laboratory LA-UR-00-2532; 16 October 2000



(a) initial lattice

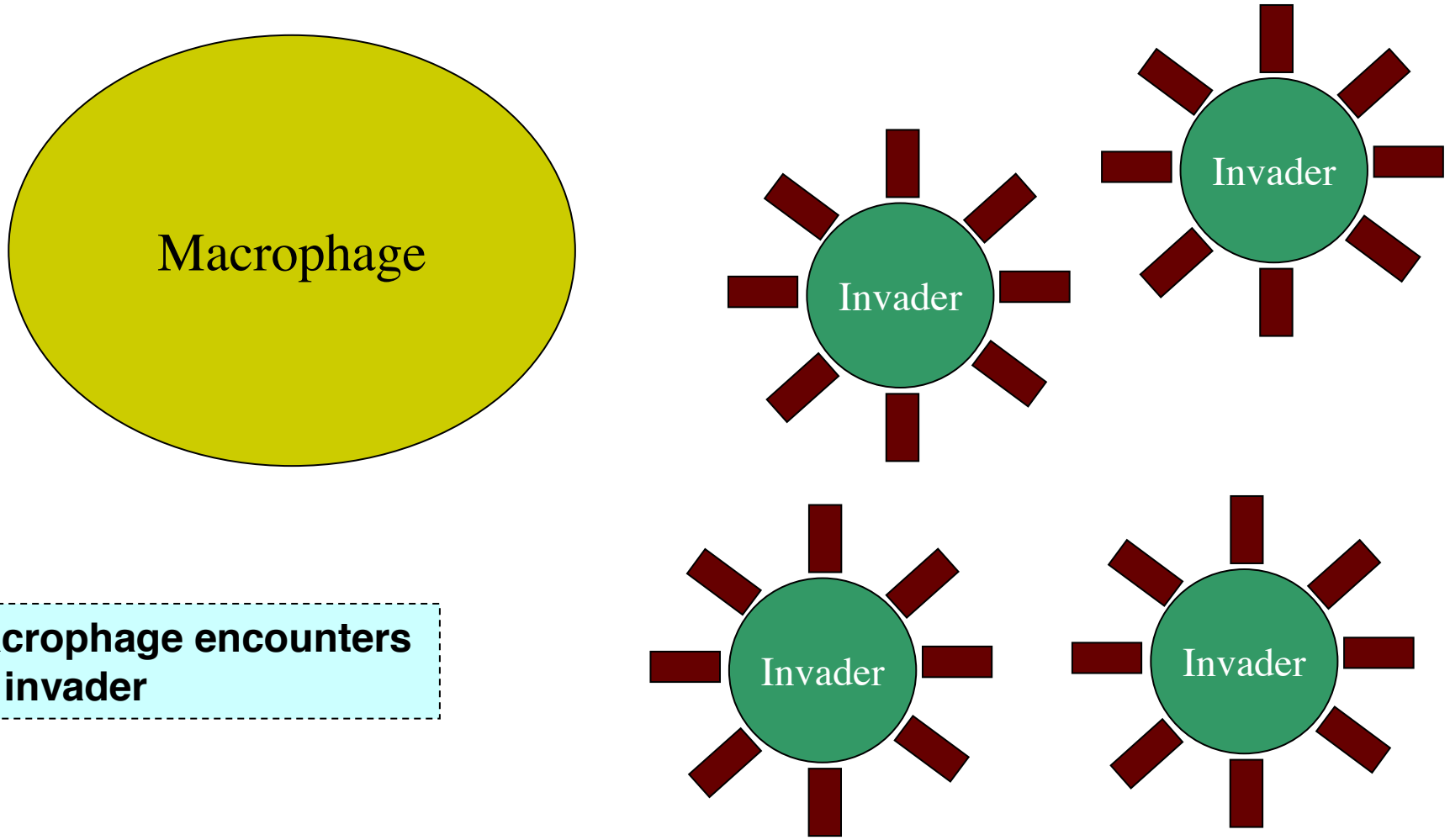


(b) propagation



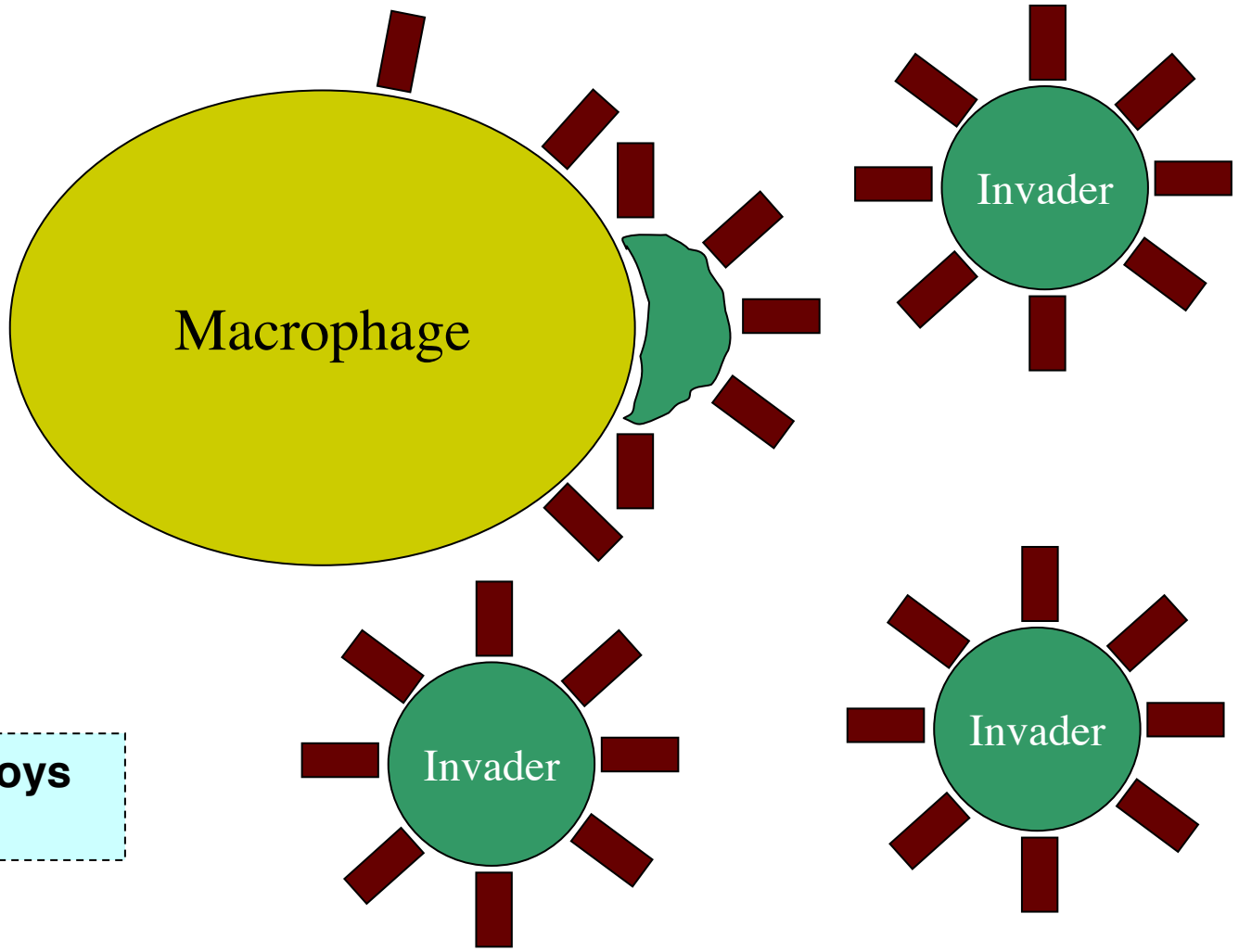
(c) collision handling

Immune System Signaling (abridged)



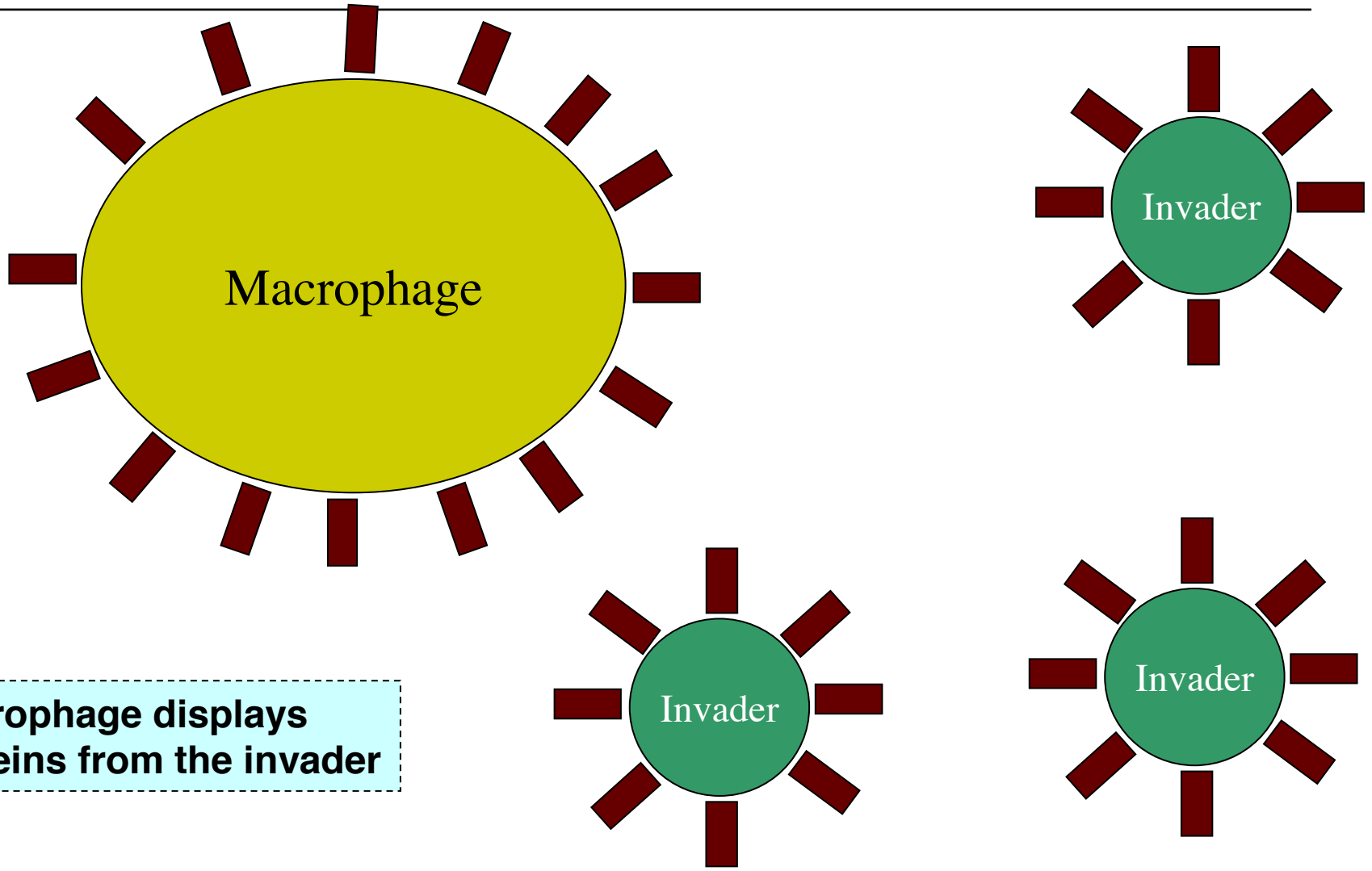
Macrophage encounters an invader

Immune System Signaling (abridged)



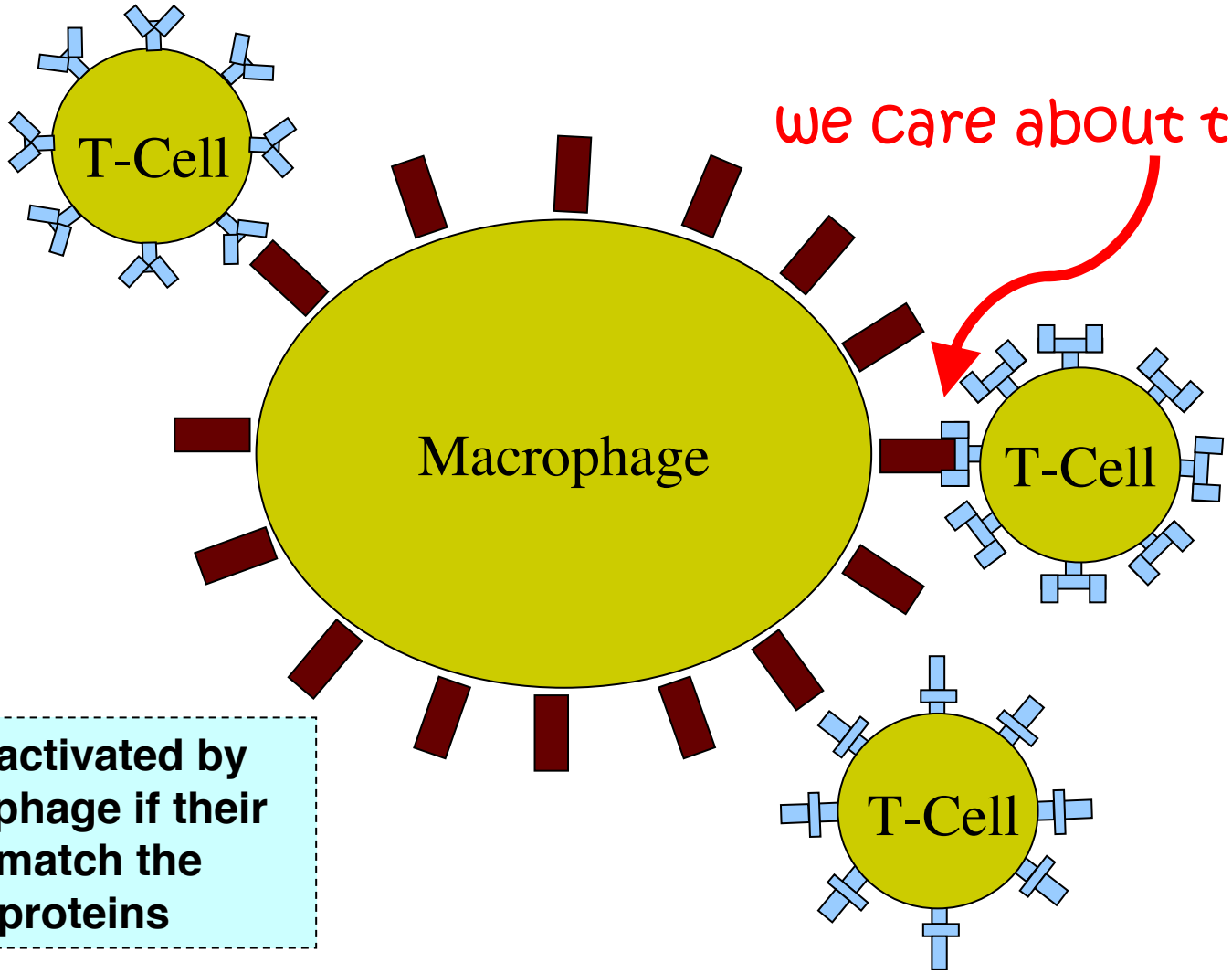
Macrophage destroys the invader

Immune System Signaling (abridged)



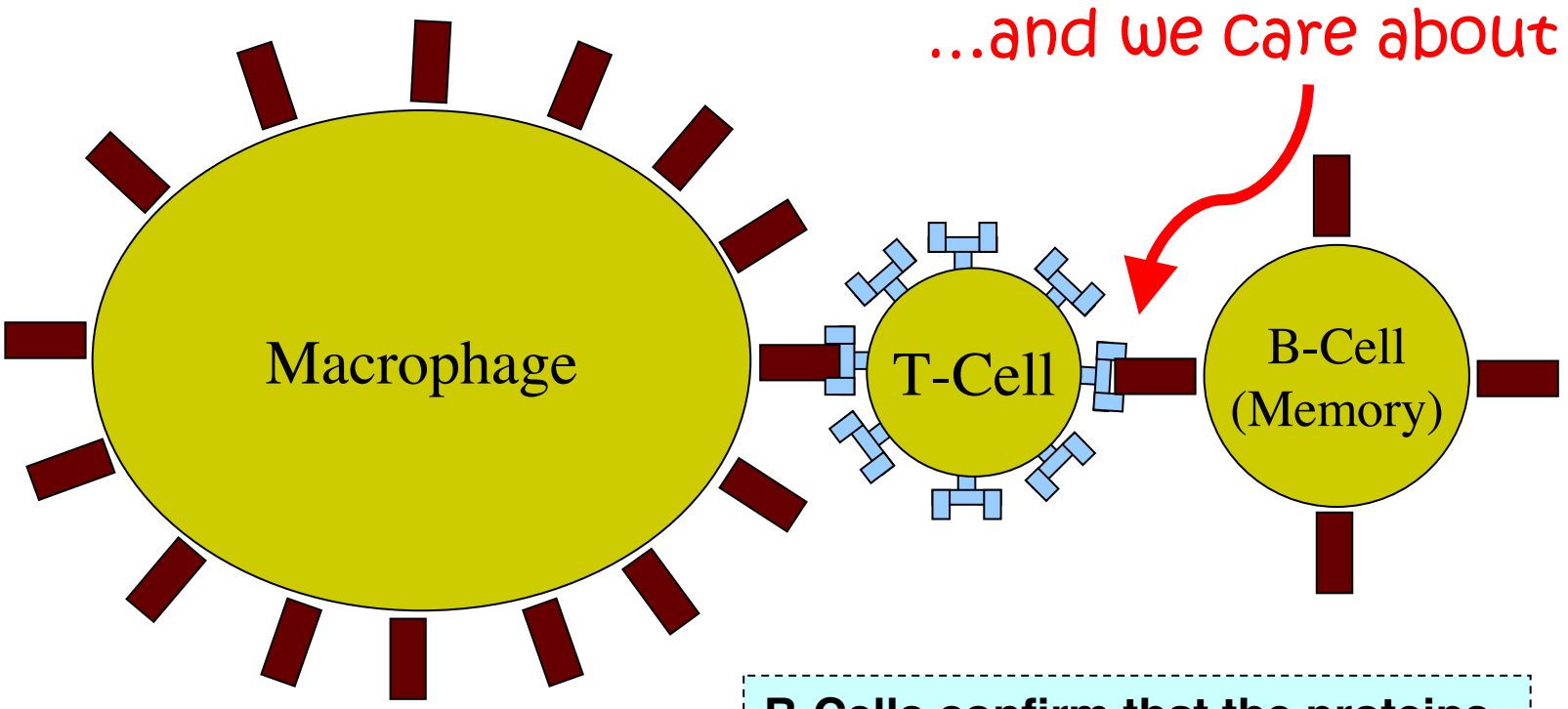
Macrophage displays proteins from the invader

Immune System Signaling (abridged)



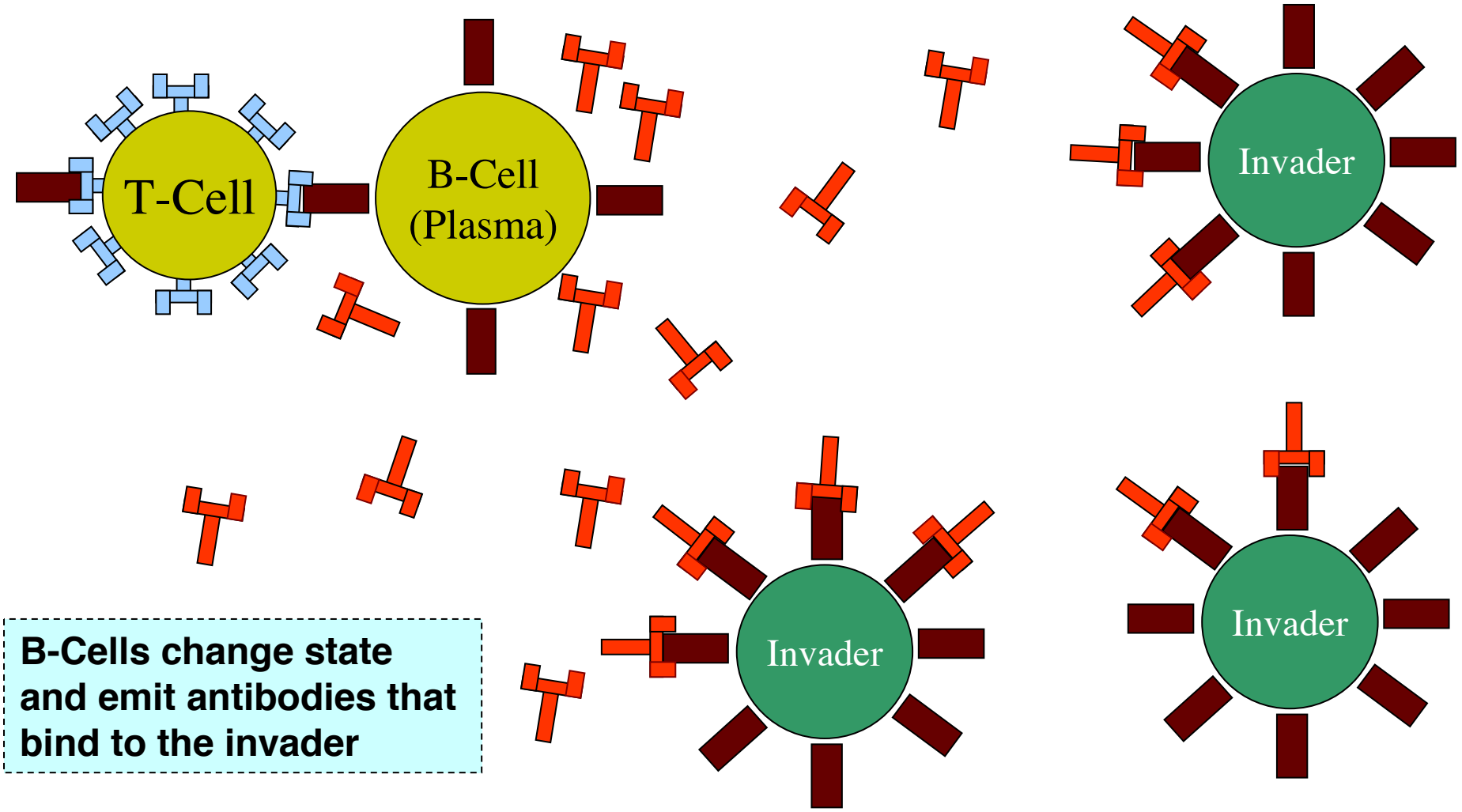
T-Cell are activated by the macrophage if their receptors match the displayed proteins

Immune System Signaling (abridged)



B-Cells confirm that the proteins are from a pathogen encountered previously.

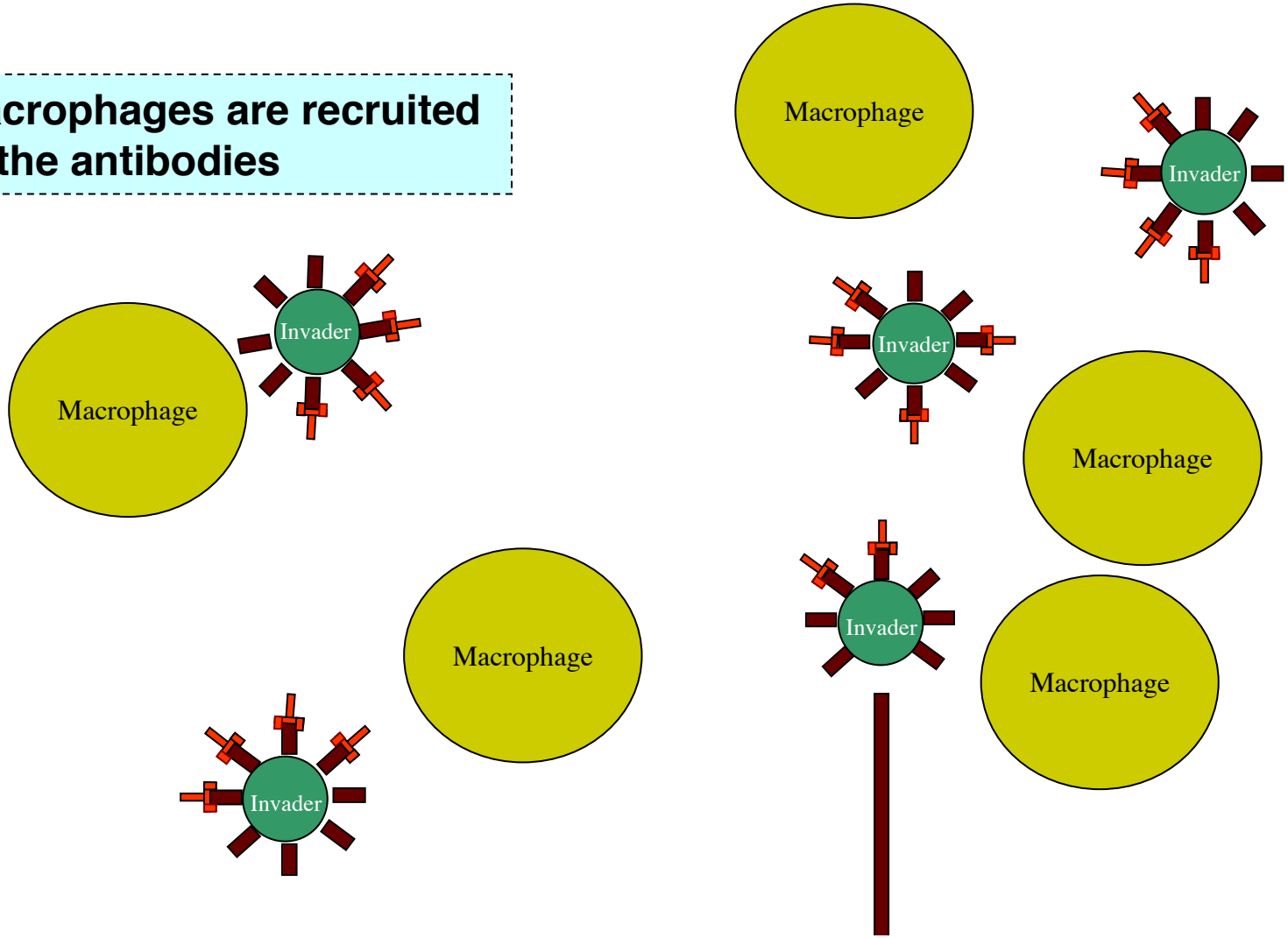
Immune System Signaling (abridged)



B-Cells change state and emit antibodies that bind to the invader

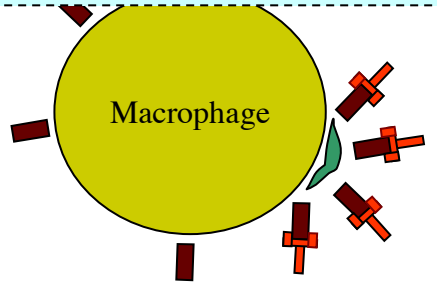
Immune System Signaling (abridged)

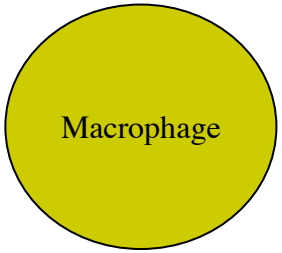
Macrophages are recruited to the antibodies

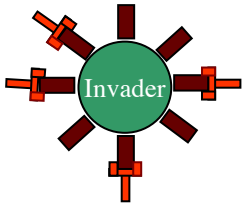


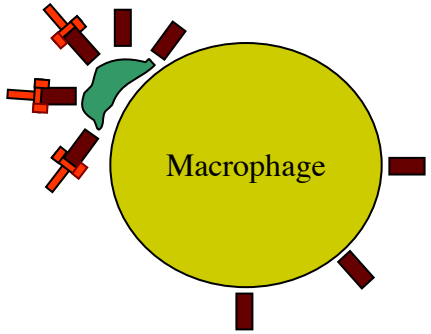
Immune System Signaling (abridged)

Recruited macrophages destroy the invaders and display their proteins.

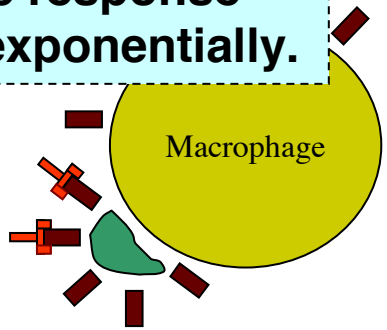


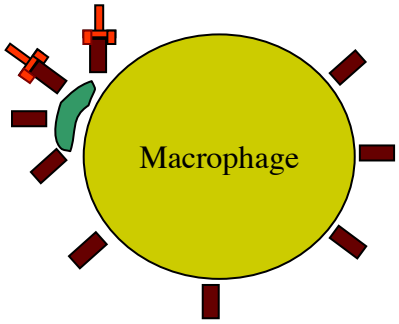




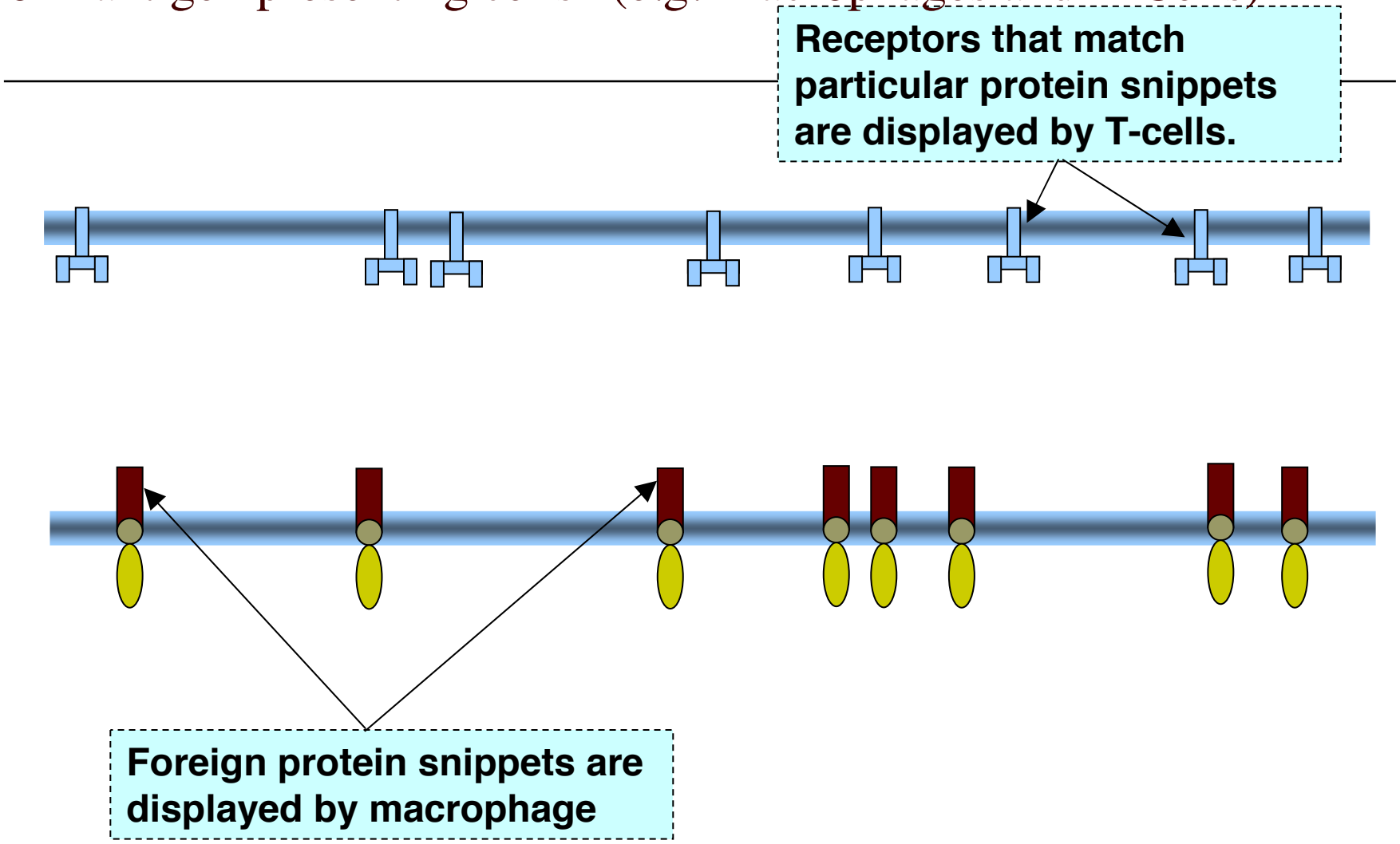


The cycle repeats and the immune response increases exponentially.





In vivo, T cells are stimulated by monovalent binding to ligands on “antigen presenting cells” (e.g. Macrophages and B-Cells)



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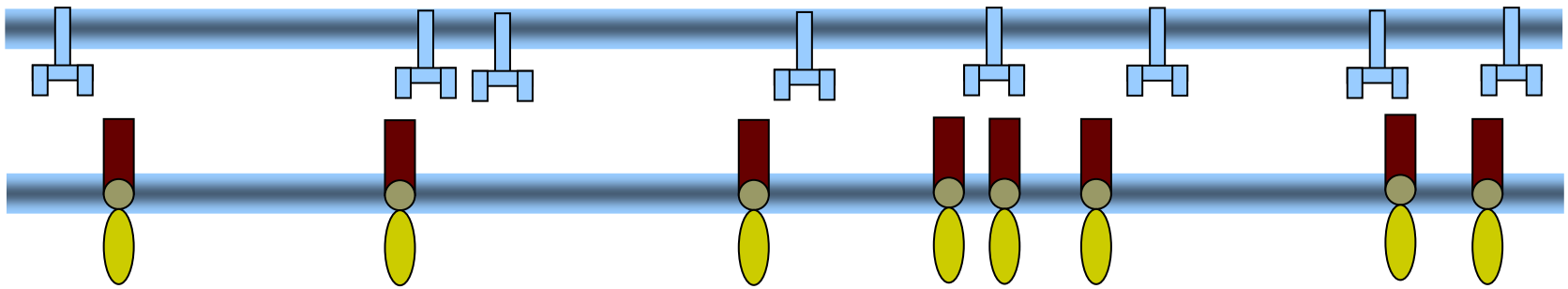

The macrophage comes into contact with various T-cells.

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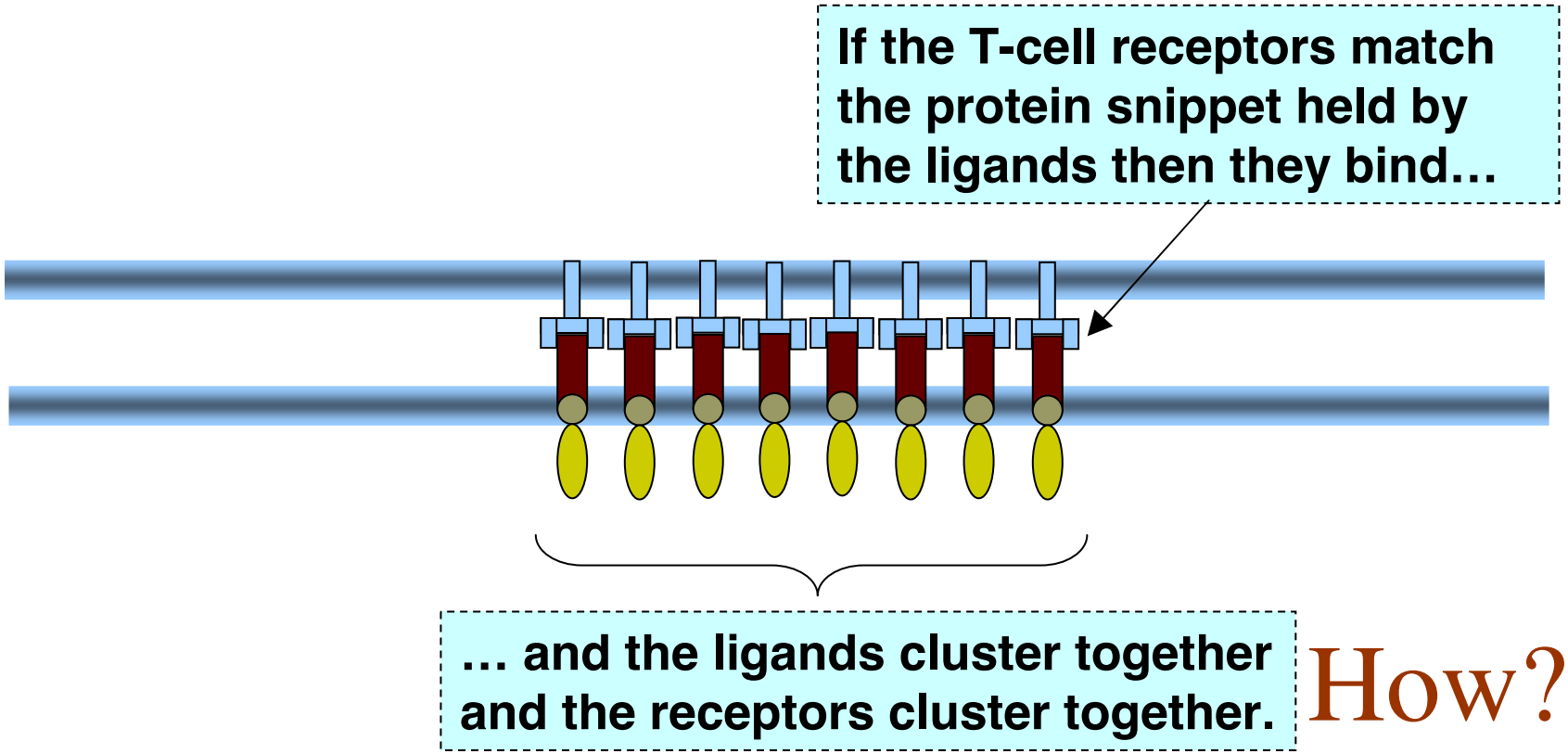
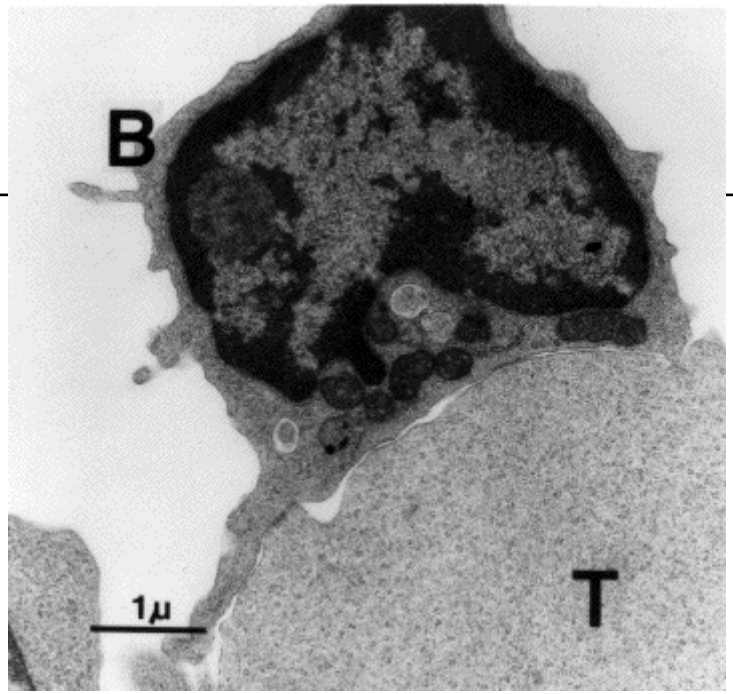
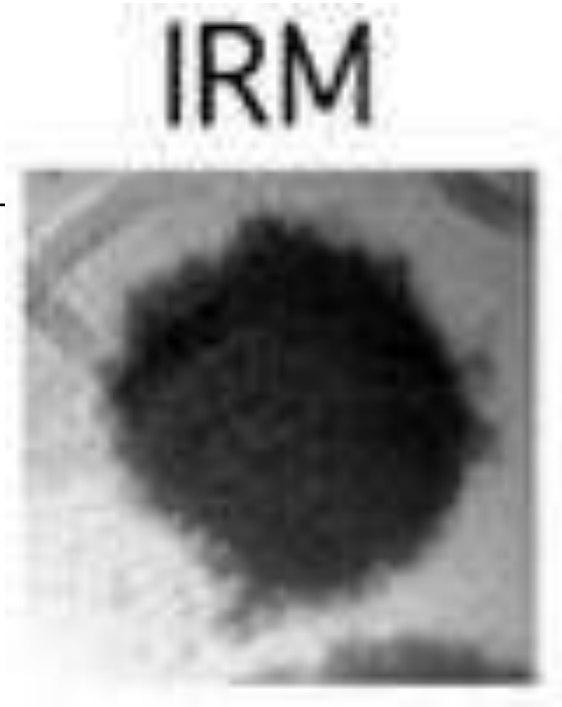






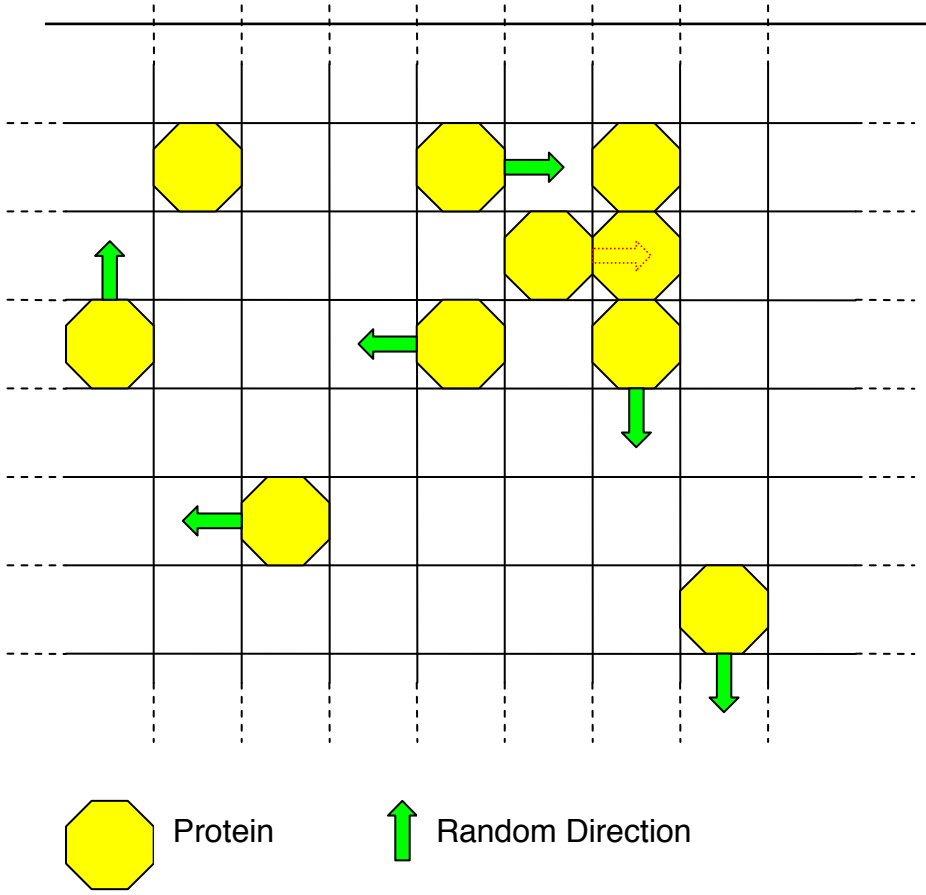
Our hypothesis: Cross Membrane binding between ligand-receptor pairs serves to combine the attractive forces between proteins in their own membranes. This would allow receptor or ligand groups that by themselves are do not cluster to “sum” the attractive forces and cluster.

Sounds simple but we can’t predict how strong the inter-membrane force needs to be in relation to the intra-membrane forces to cause phase separation. So model it!

Our Approach

- Write a model of phase separation on a single membrane
- Confirm that our results match those of previous phase transition models
- Implement two copies of the single membrane model and bring them into contact
- Add a cross-membrane binding force
- Under what circumstances do we get phase separation?

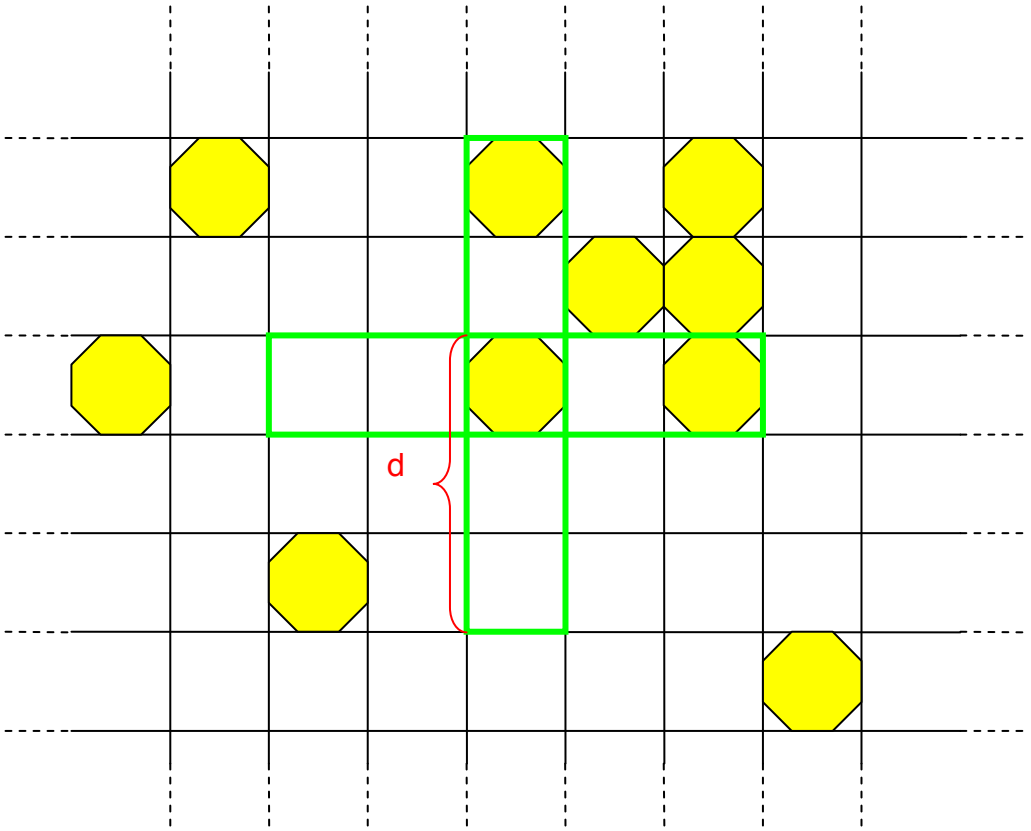
Metropolis Monte Carlo



ε = Favorable contact energy (in kT) between neighboring proteins.

- *n* x *n* toroidal lattice
- Each site on the lattice can hold a single protein
- At each discrete time-step all proteins choose a random direction to move
- If the energy is reduced the motion is accepted.
- Otherwise the motion is accepted with probability $e^{(-\Delta E/kT)\varepsilon}$.
- Repeat until we are confident that the system is in equilibrium

Measuring Phase Separation – Spatial Autocorrelation



- Autocorrelation Function g(*d*)
- Choose a protein and count the number of proteins at distance *d (then ÷ 4 .)*

The system ***probabilistically*** (Monte Carlo) enters a new lower energy configuration. The probability depends on how much the energy is decreased.

$$P = e^{-\Delta E / k_B T}$$ k_B Boltzmann Constant T Temperature

Where the energy change is given by the binding energy N_{pp} at the proposed site, s_1 verses the current site s_0.

$$\Delta E = -\varepsilon k_B T \left(N_{pp,s1} - N_{pp,s0} \right)$$

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$$\frac{P_{i \to j}}{P_{j \to i}} = \exp\left[-\Delta E_{ij} / k_B T \right]$$ Microstate reversibility: Metropolis rule.

Predictions from Theory

The protein autocorrelation will scale with binding energy as:

$$\xi \propto \frac{1}{\varepsilon_c - \varepsilon}$$

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Time spent proteins spend bound (p) vs unbound (u):

$$\frac{\overline{t_u}}{\overline{t_p}} = \frac{1-c}{c} e^{-\varepsilon_x}$$

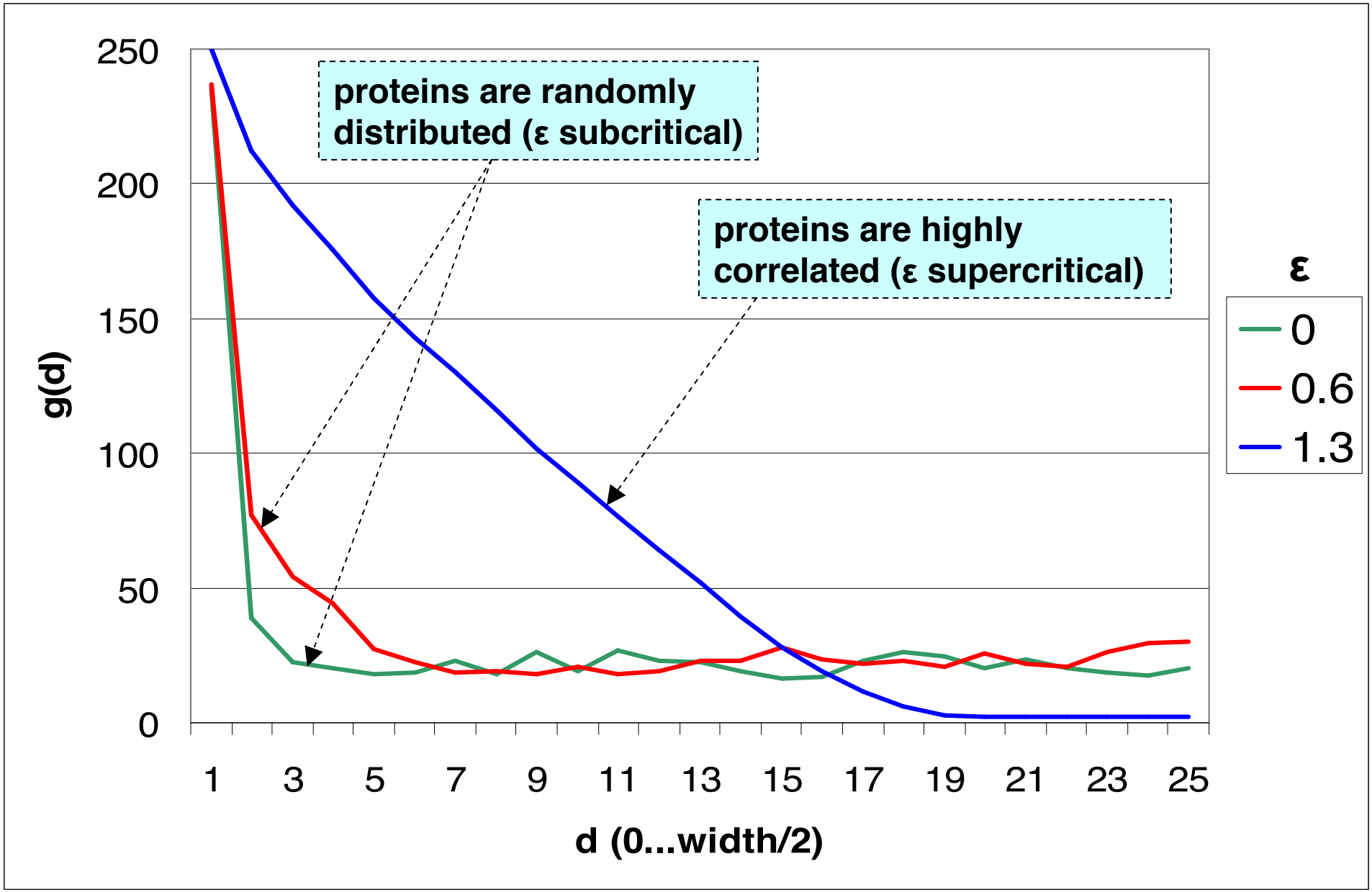
c is the concentration of proteins.

Predictions from Theory

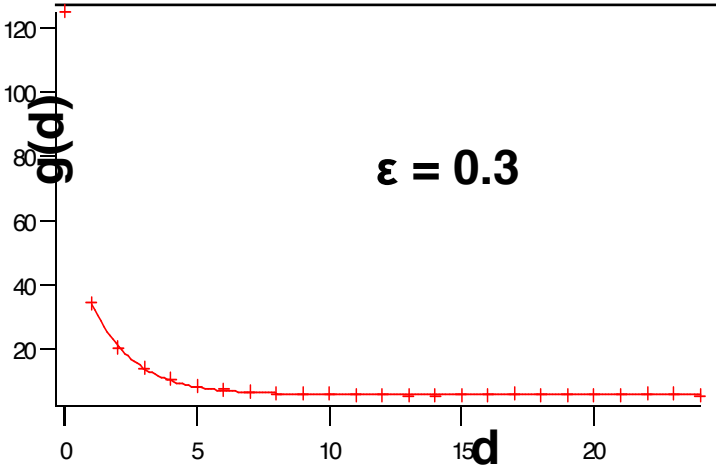
The effective interprotein interaction is:

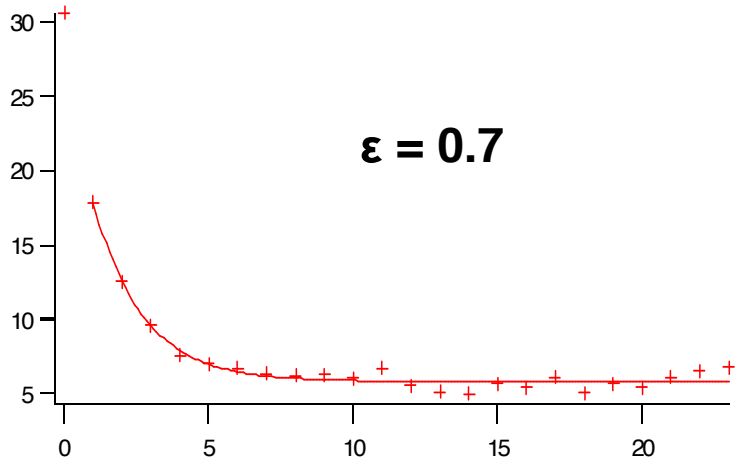
$$\varepsilon_{\mathrm{eff}} = \frac{\varepsilon\overline{t_{\mathrm{u}}} + 2\varepsilon\overline{t_{\mathrm{p}}}}{\overline{t_{\mathrm{u}}} + \overline{t_{\mathrm{p}}}} = \frac{(1-c)e^{-\varepsilon_x} + 2c}{(1-c)e^{-\varepsilon_x} + c}\varepsilon$$

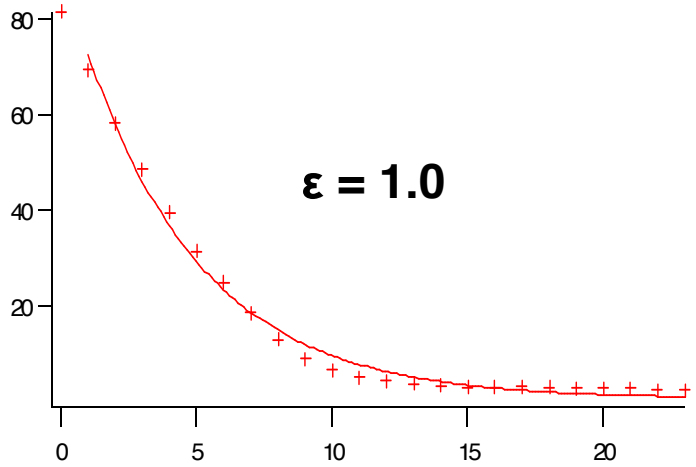
Correlation Functions for Three Values of ε

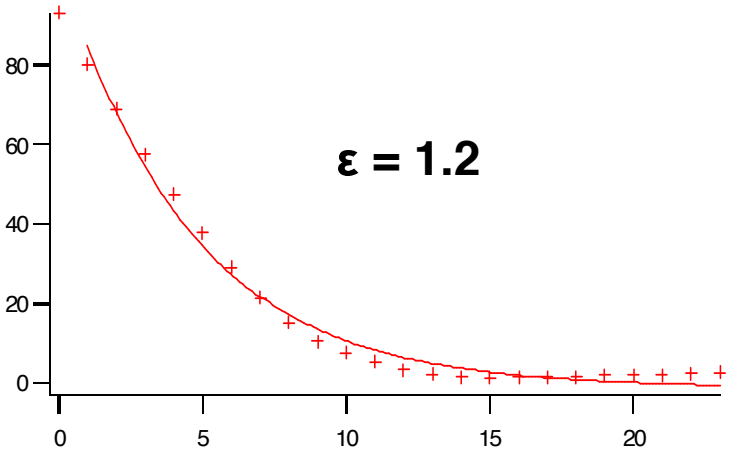


Fit Correlation Functions to an Exponential $y = C_1 e^{C_2 x}$ (fit deteriorates as critical epsilon reached)

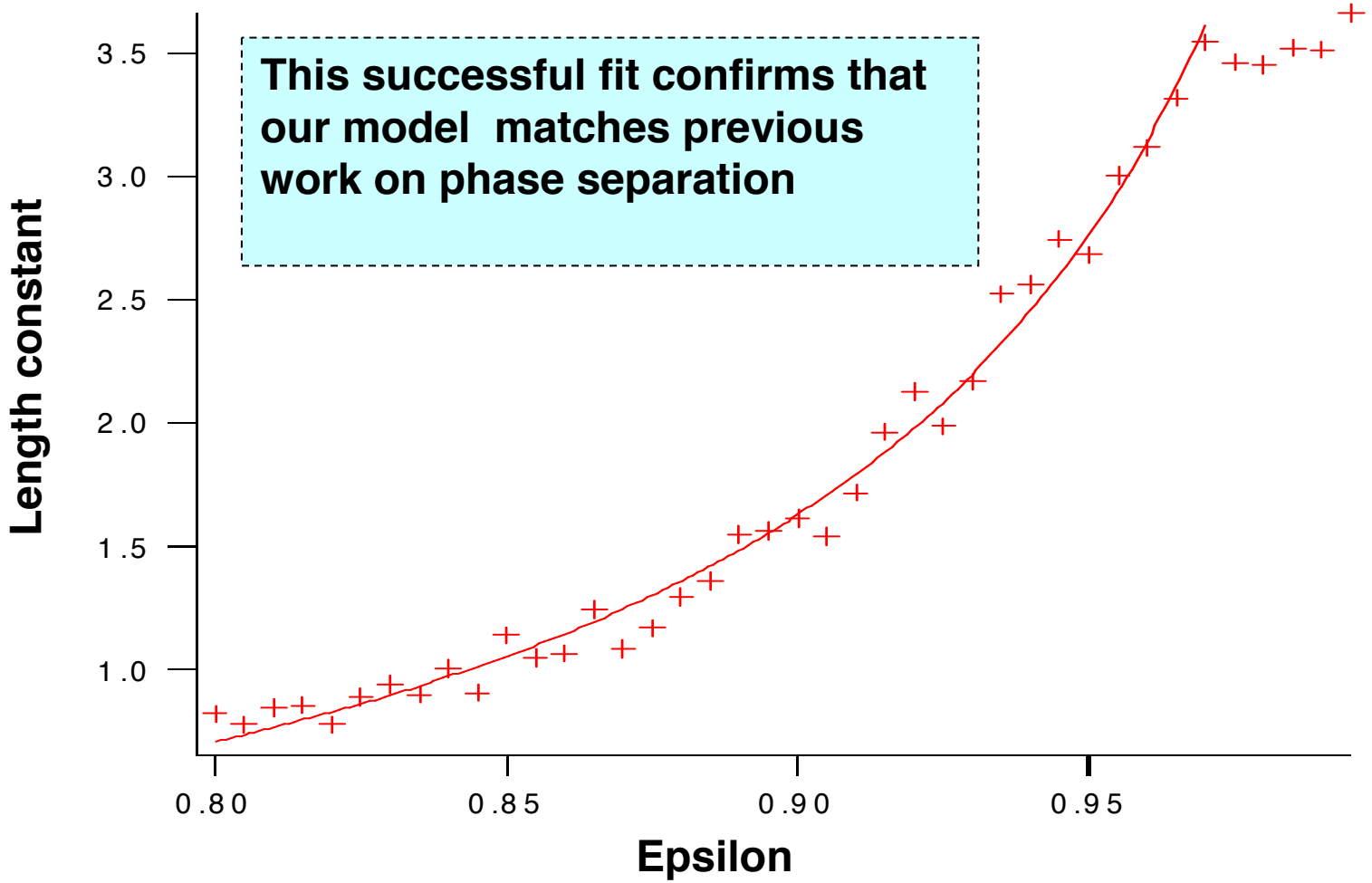






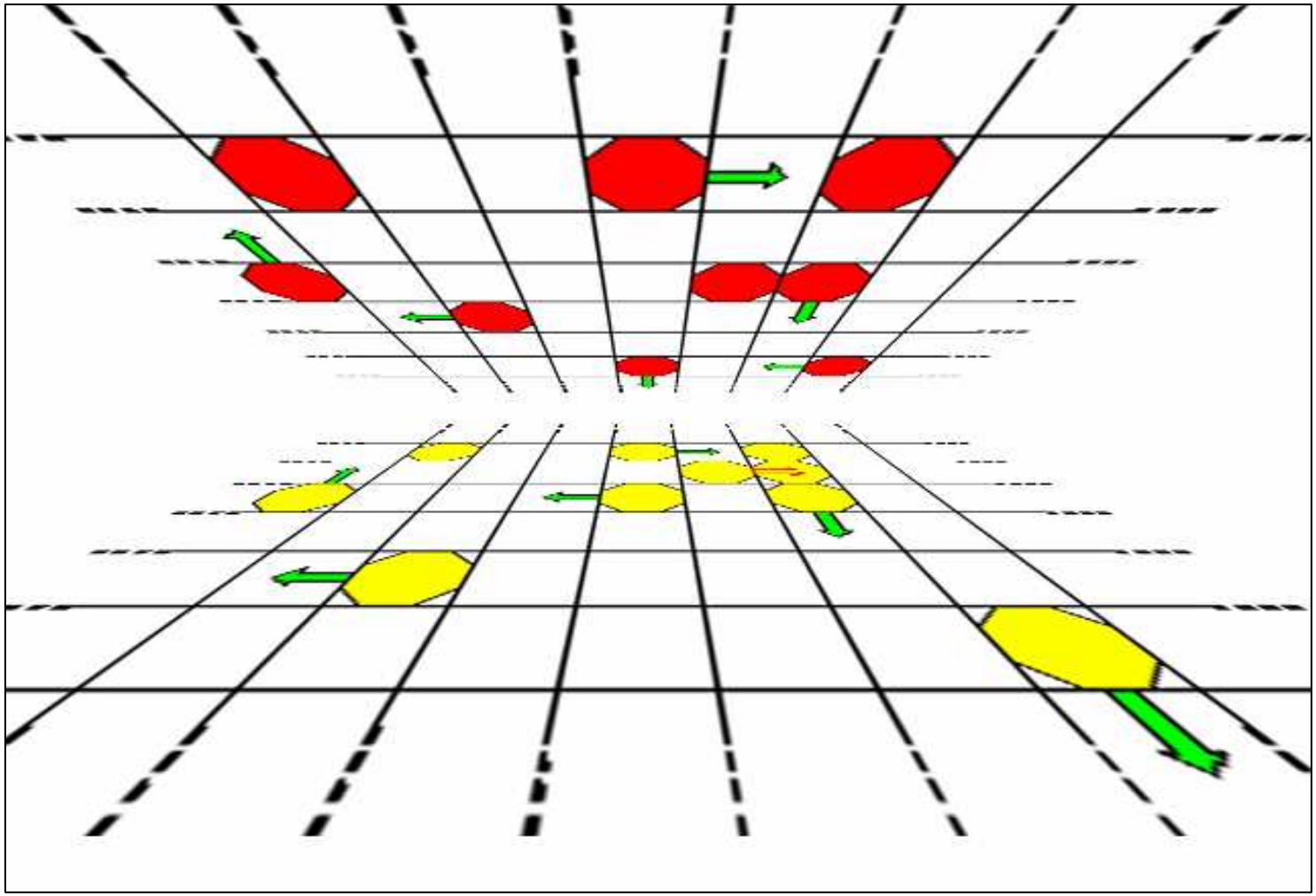


Fit exponential length constants to $\frac{C_1}{\varepsilon - \varepsilon_c} + C_2$ *



* Gould H., and J. Tobochnik An Introduction to Computer Simulation Methods: Applications to Physical Systems, 1996

Two Membrane Model

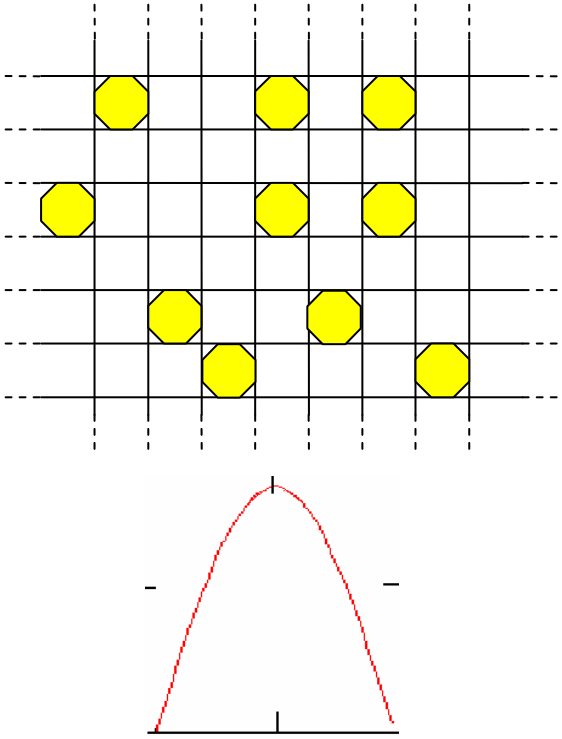


Density variance as a measure of phase separation

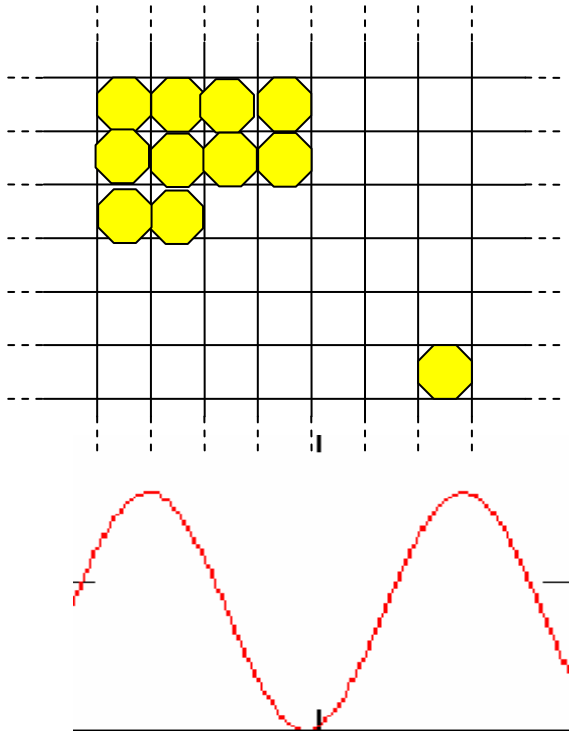
Calculating the autocorrelation, exponents, and critical exponents is too slow

Instead: calculate the protein density for all overlapping 3x3 squares on the lattice

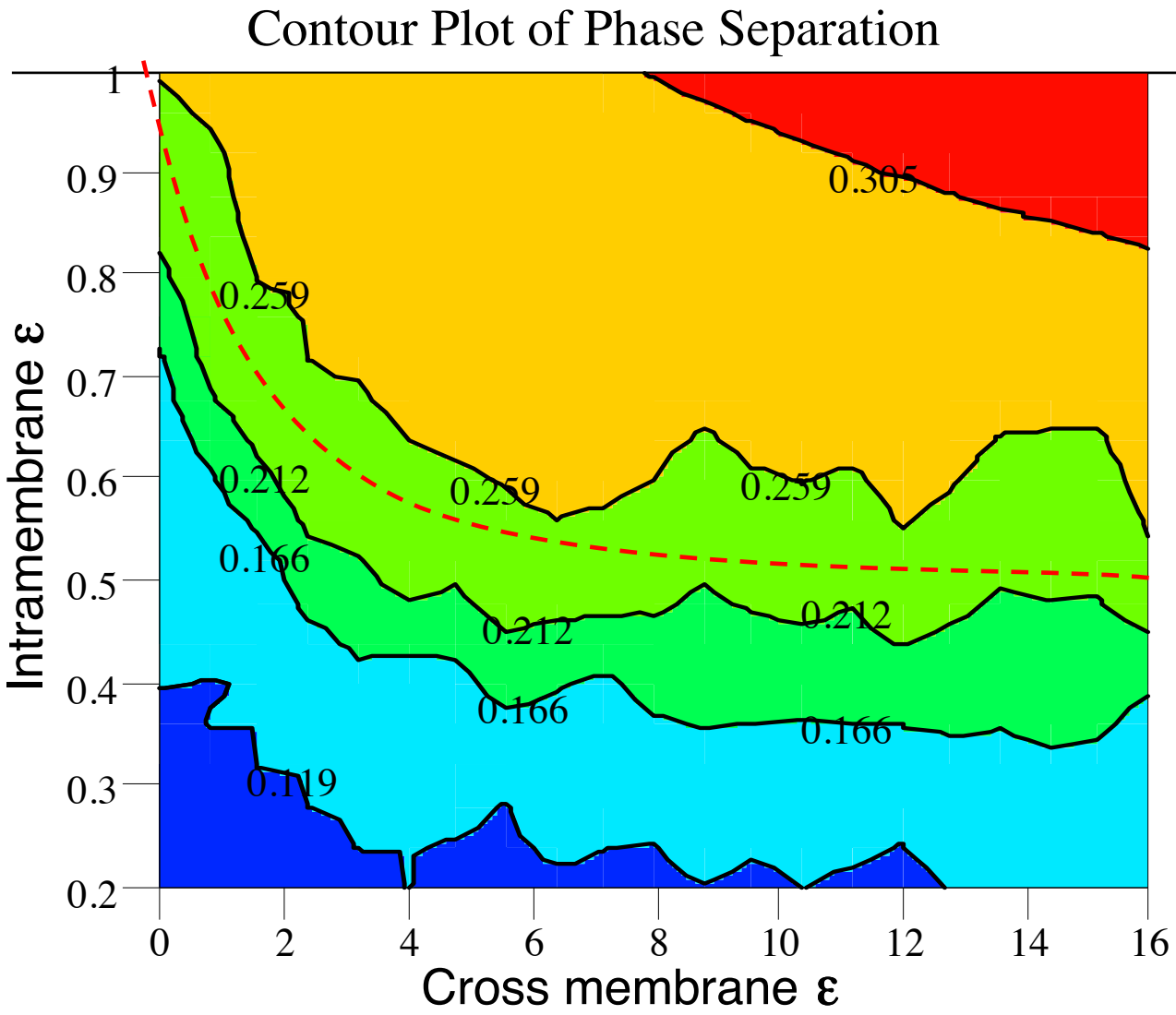
Standard deviation is a measure of phase separation



Low σ, one phase



High σ, two phase



Complete phase separation occurs at 0.27

Random protein distributions have been observed to have values of between 0.09 and 0.105

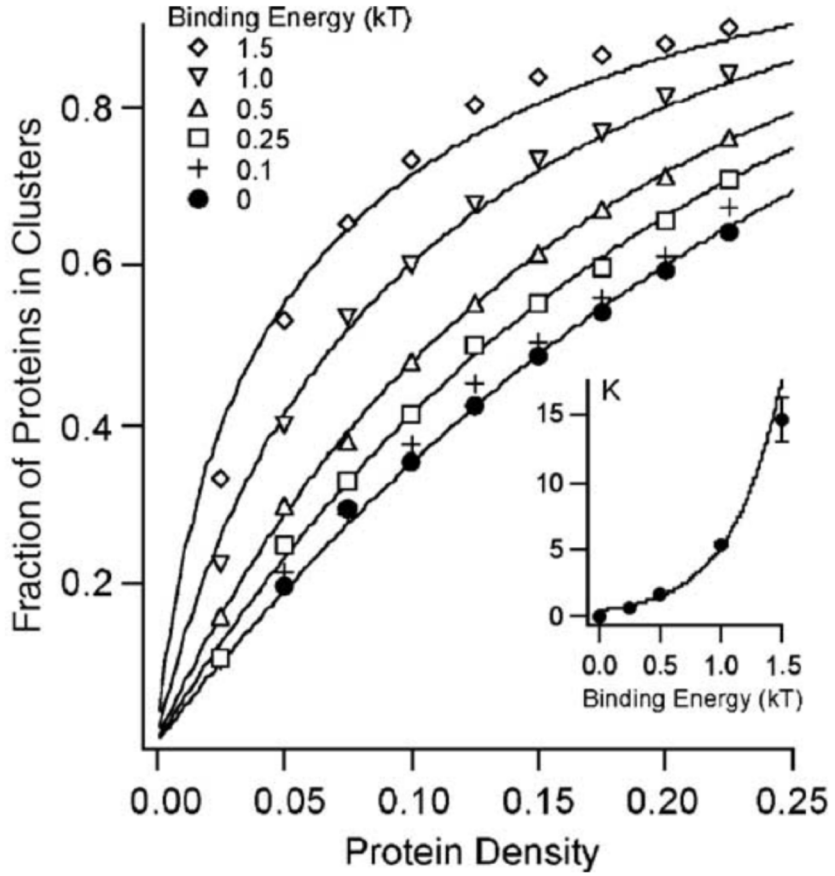


Fig. 2. Fraction of proteins in clusters (dimers or higher aggregates), as a function of protein density, for various attractive interaction energies. The clustered fraction was fit to a background level of statistical aggregation, plus a mass action term (a dimerization equilibrium). The dimerization constant K is plotted in the inset versus the binding energy, and shows the expected exponential dependence. Exact correspondence is not expected, because higher order aggregation is possible. Data from 100×100 lattice run for 10,000 iterations.

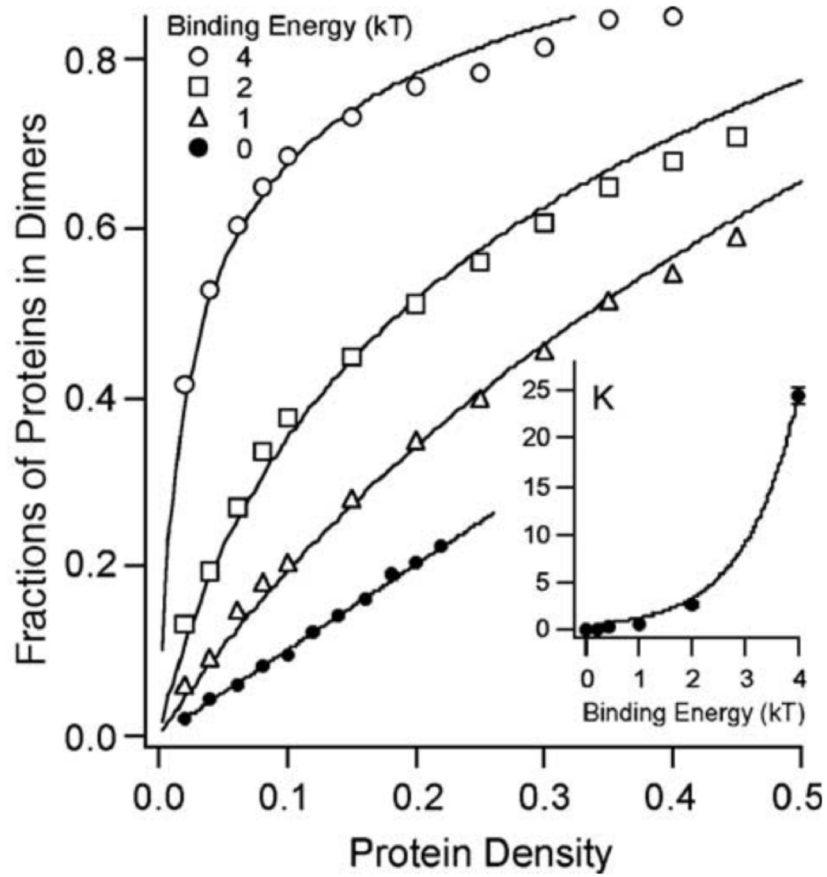


Fig. 3. Fraction of proteins in *intermembrane* dimers as a function of protein density in both membranes. At zero interaction energy, the fraction of dimers is the same as the protein density, as expected for random associations. The dimer concentration can be well fit by the sum of the background association, plus a mass action term. The dimerization constant for the mass action term is well fit to an exponential in binding energy, inset.

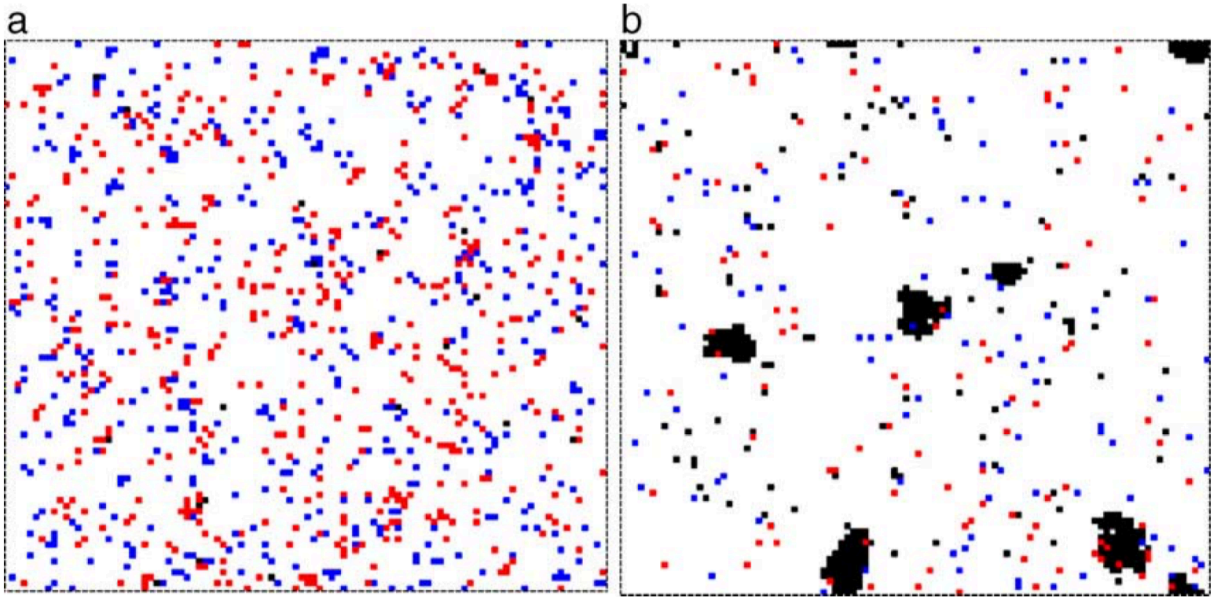


Fig. 4. (a) left: 100×100 double lattice at step 6500 with a protein concentration of 0.05 on each lattice. Intra-lattice protein interaction energy is 0.6 $k_{\mathrm{B}}T$ and the intermembrane interaction energy is zero. At this interaction energy, large clusters are never observed. (b) right: The same lattice configuration as in (a) but with an added intermembrane interaction energy of 5.0 $k_{\mathrm{B}}T$. Note the formation of large clusters as a consequence of the added intermembrane interaction.

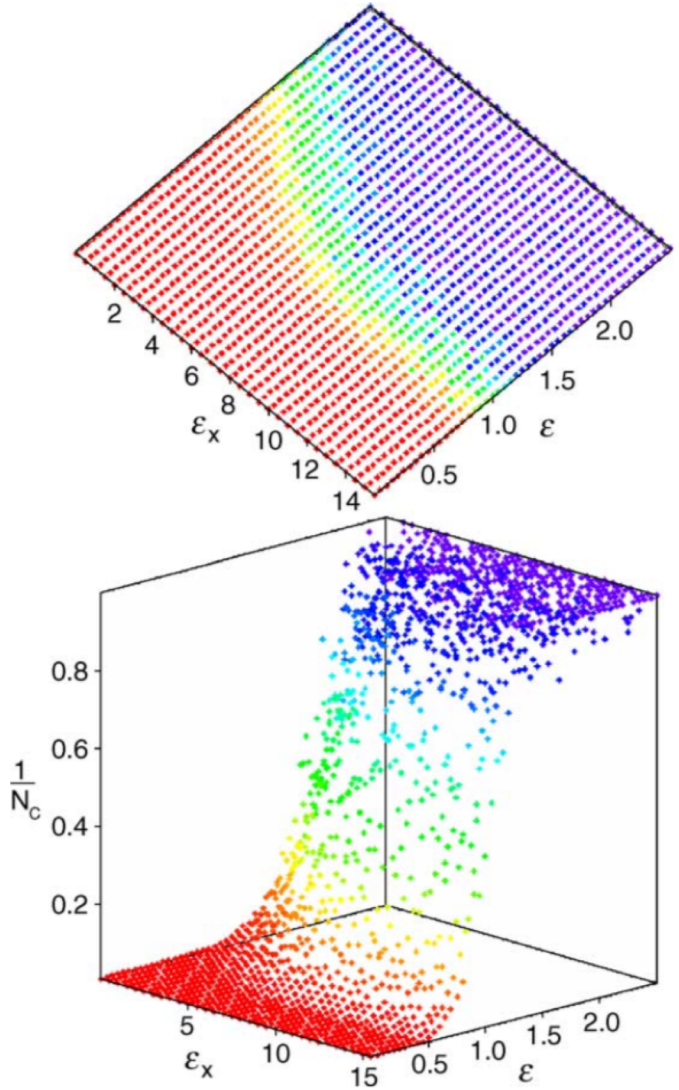


Fig. 5. The reciprocal of the mean number of clusters (per membrane) in the two-membrane model, as a function of the intra- and intermembrane protein interaction energies. Each of the two 100×100 square lattices hosted 500 proteins, a density of 0.05. (Bottom) a 3D plot; (Top) same data, viewed from above. Color coding helps to identify the range of parameters that give strong clustering: blue and purple colors correspond to fewer than 2 clusters per membrane in the ensemble. The model was run for 15,000 iterations. To reduce the statistical variation, $1/N_C$ was averaged over 5 runs.

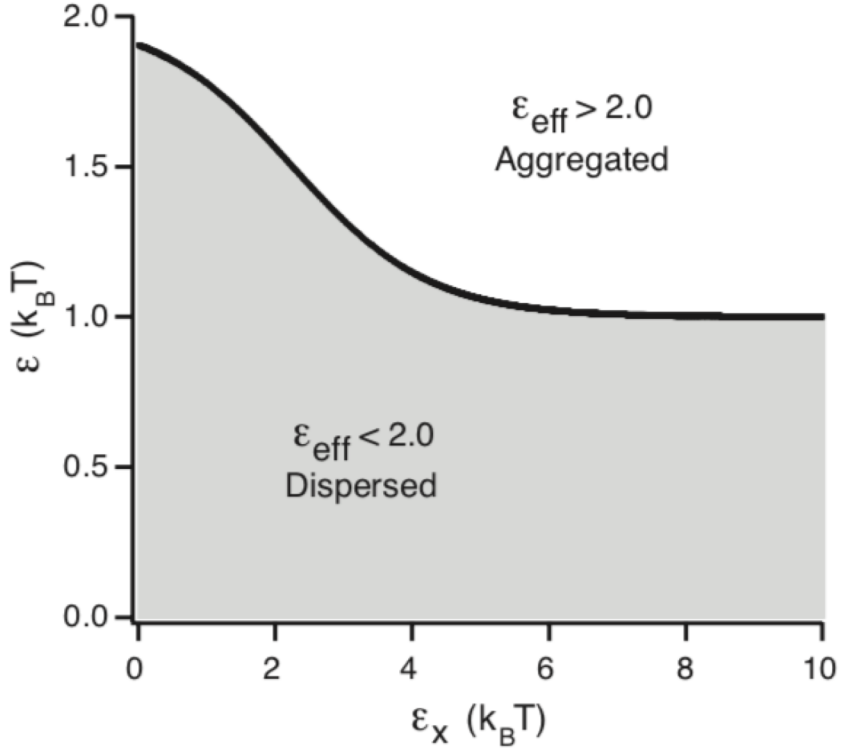
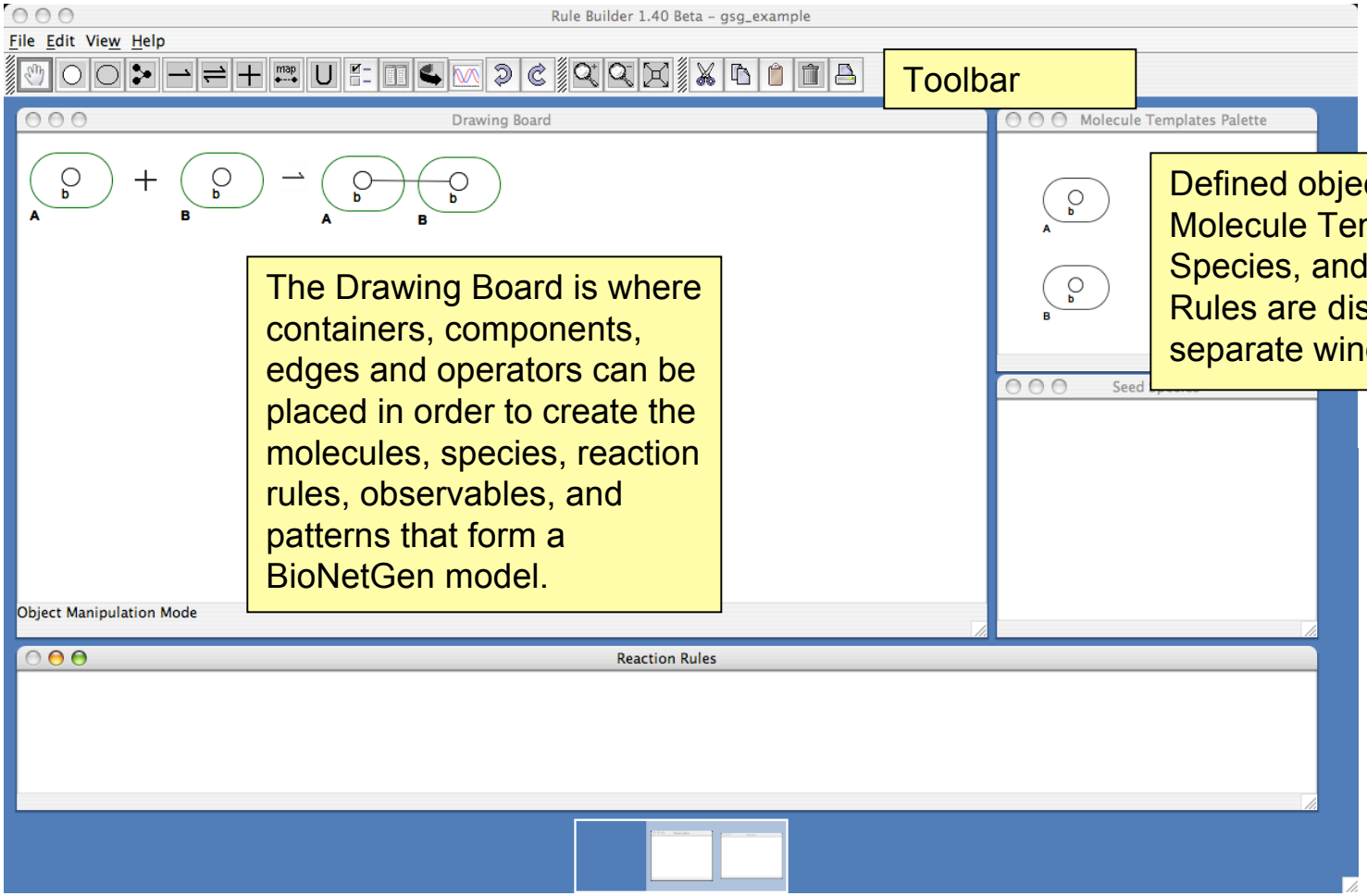
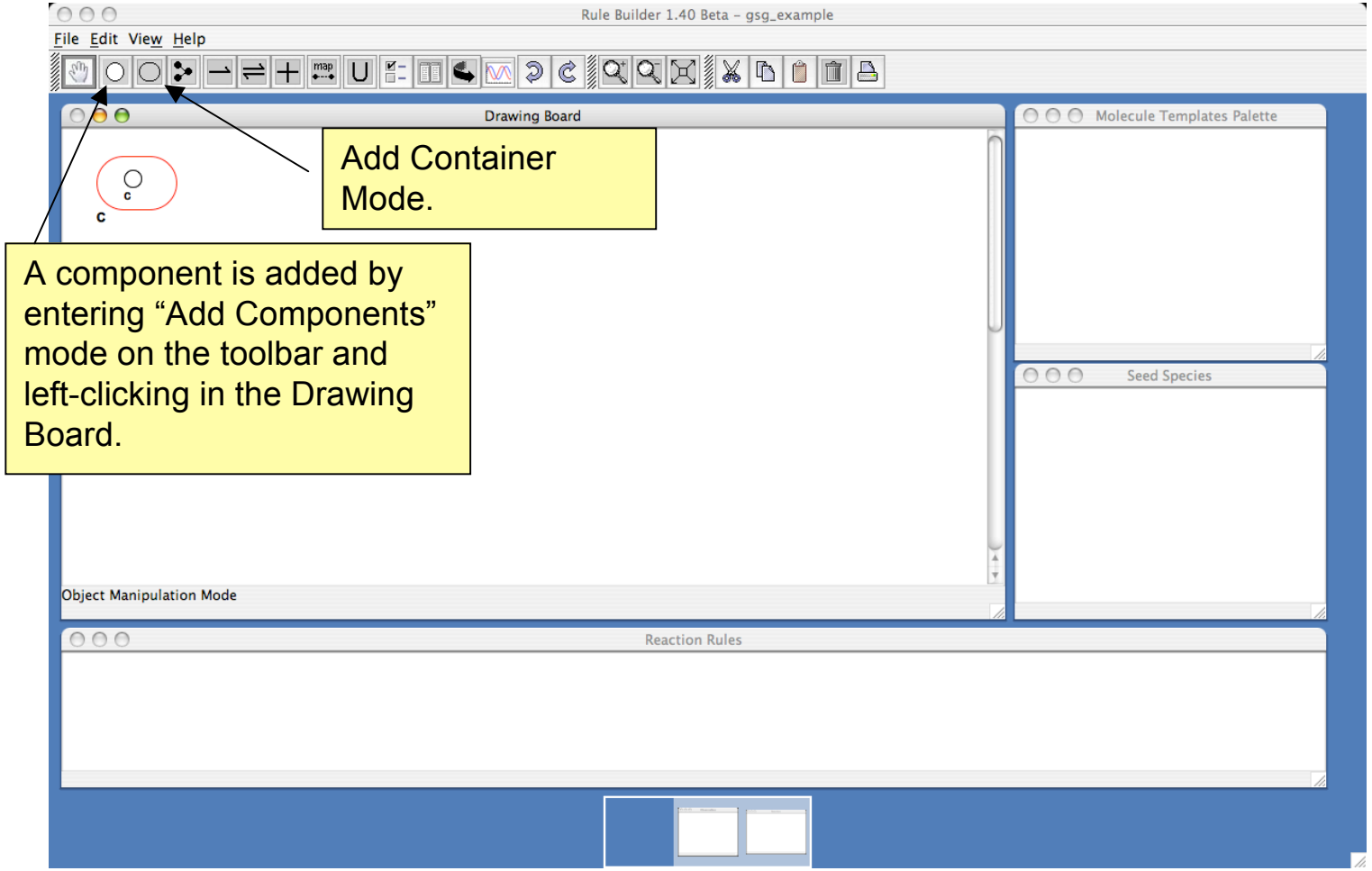


Fig. 6. The strengths of the intra-(ε) and intermembrane (ε_x) protein interaction energies (in k_BT) required to give an effective interprotein interaction of 2 k_BT, according to a simple "mean field" estimate. 2 k_BT is the threshold for receptor aggregation at this concentration (5%). The line should be compared with the boundary between aggregated (blue) and dispersed (red) protein phases in Fig. 5, Top.

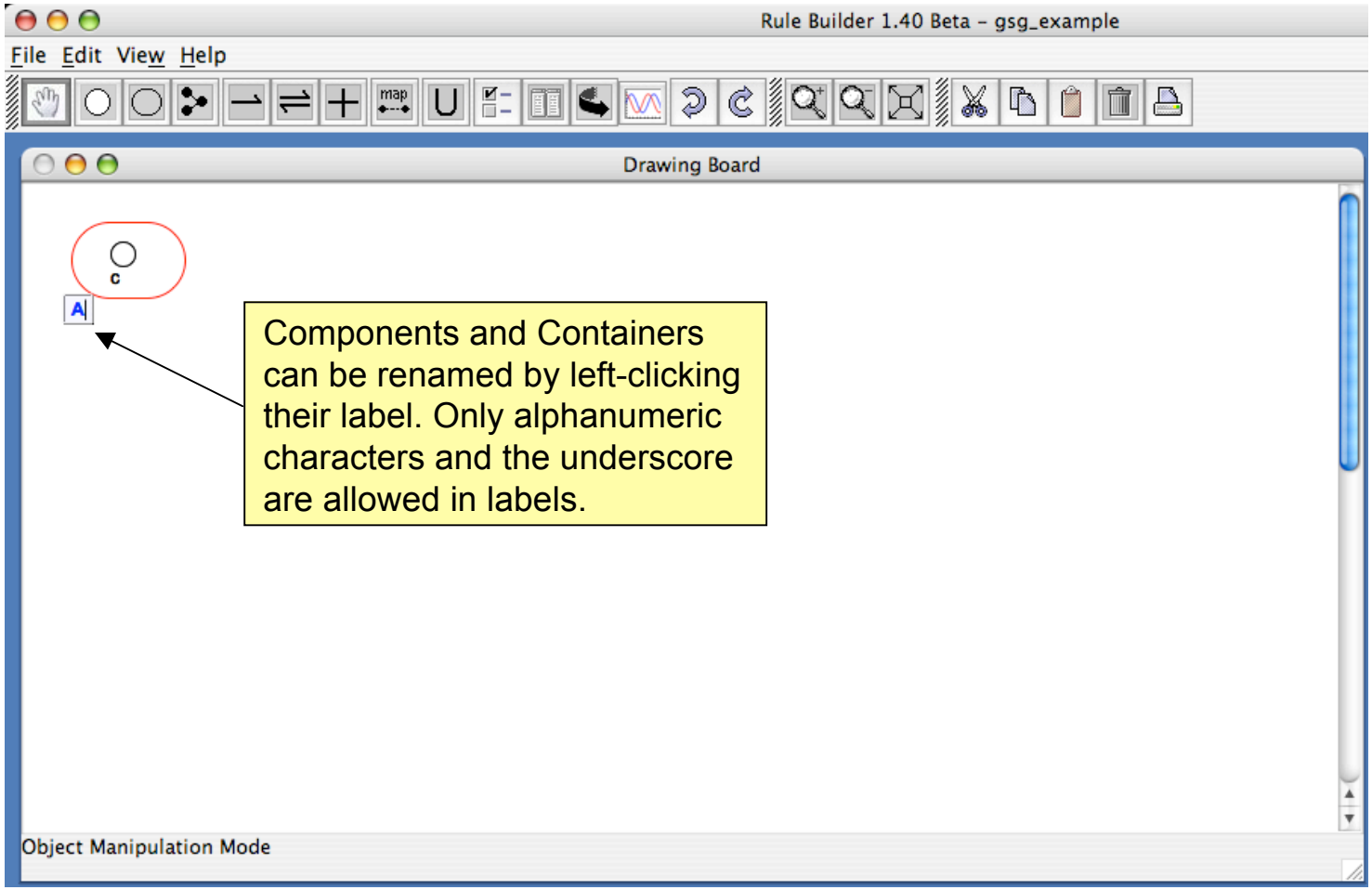
RuleBuilder Layout



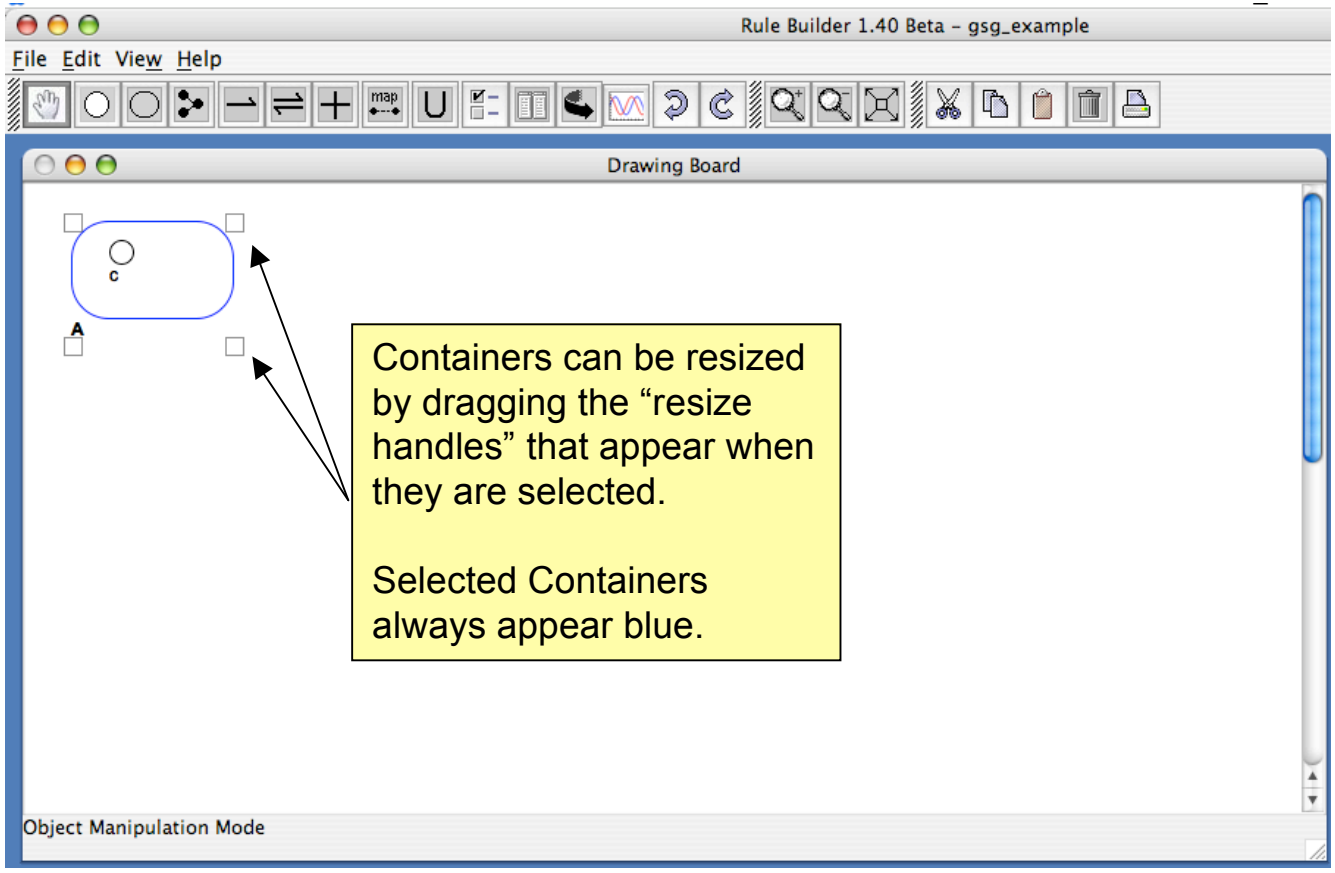
Adding Containers and Components



Renaming Components and Containers

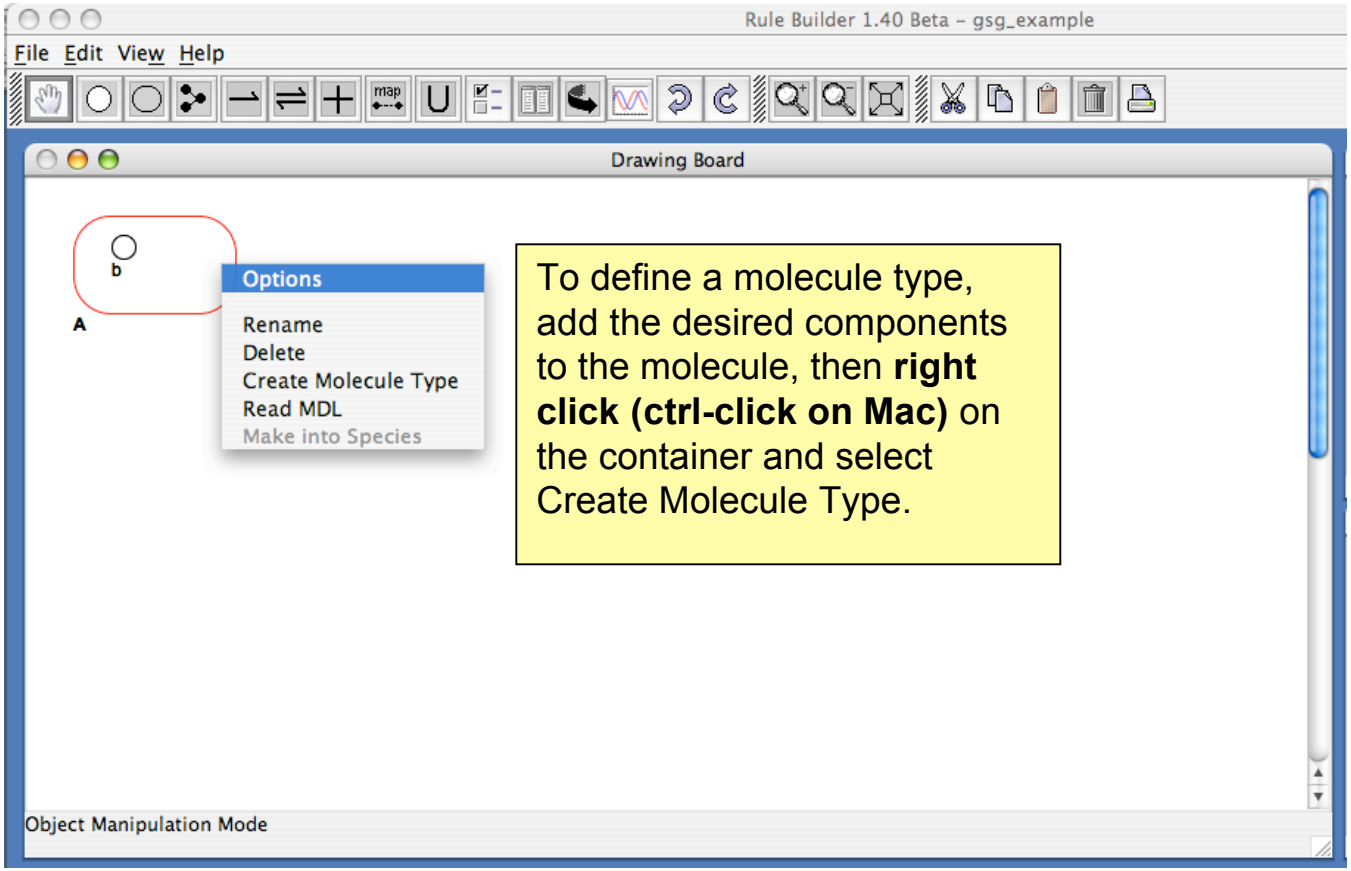


Resizing Containers



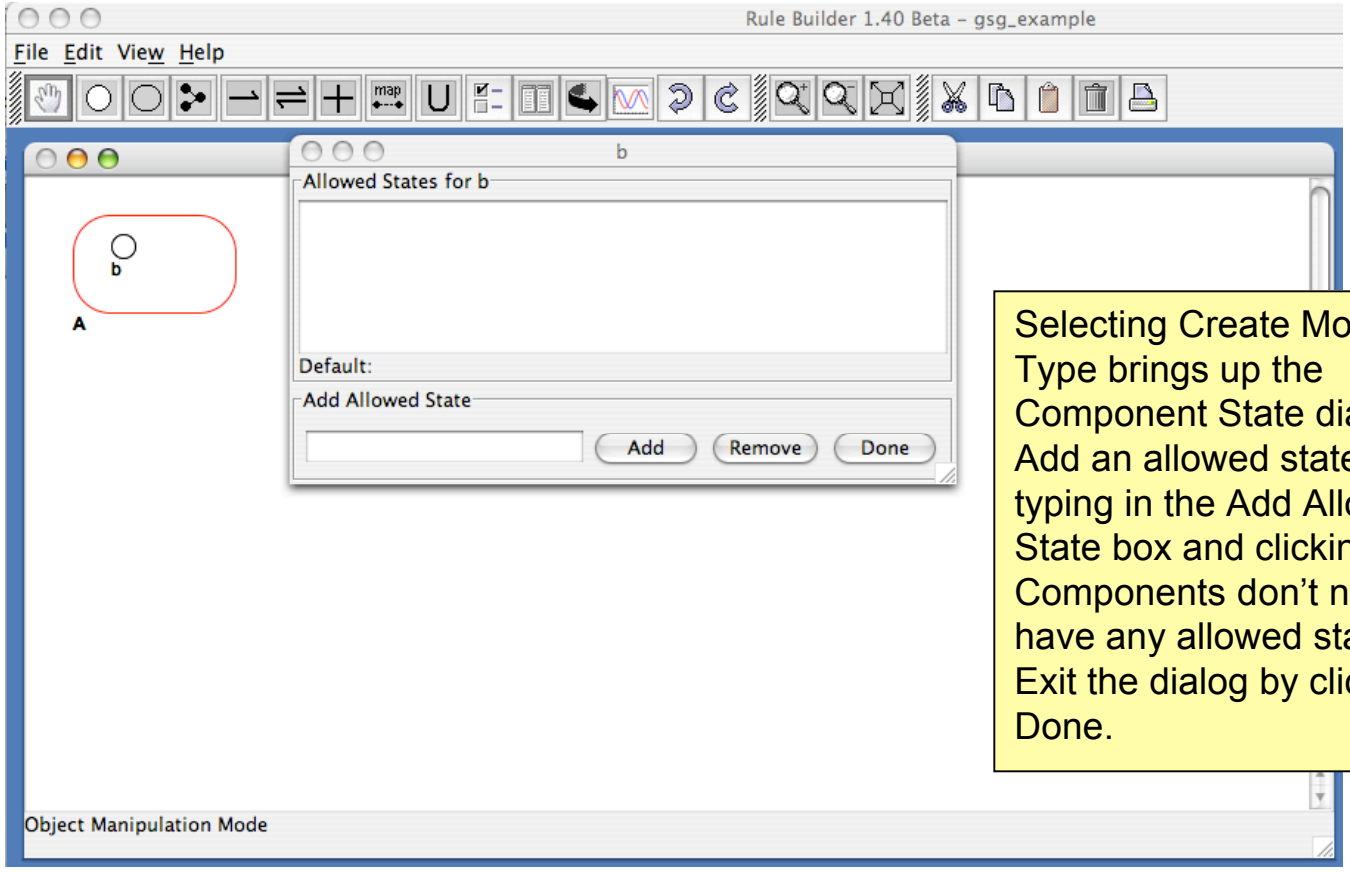
Creating Molecule Types

Molecules used in a model have to be defined and registered as a “Molecule Type” before they can be used in reaction rules and species.



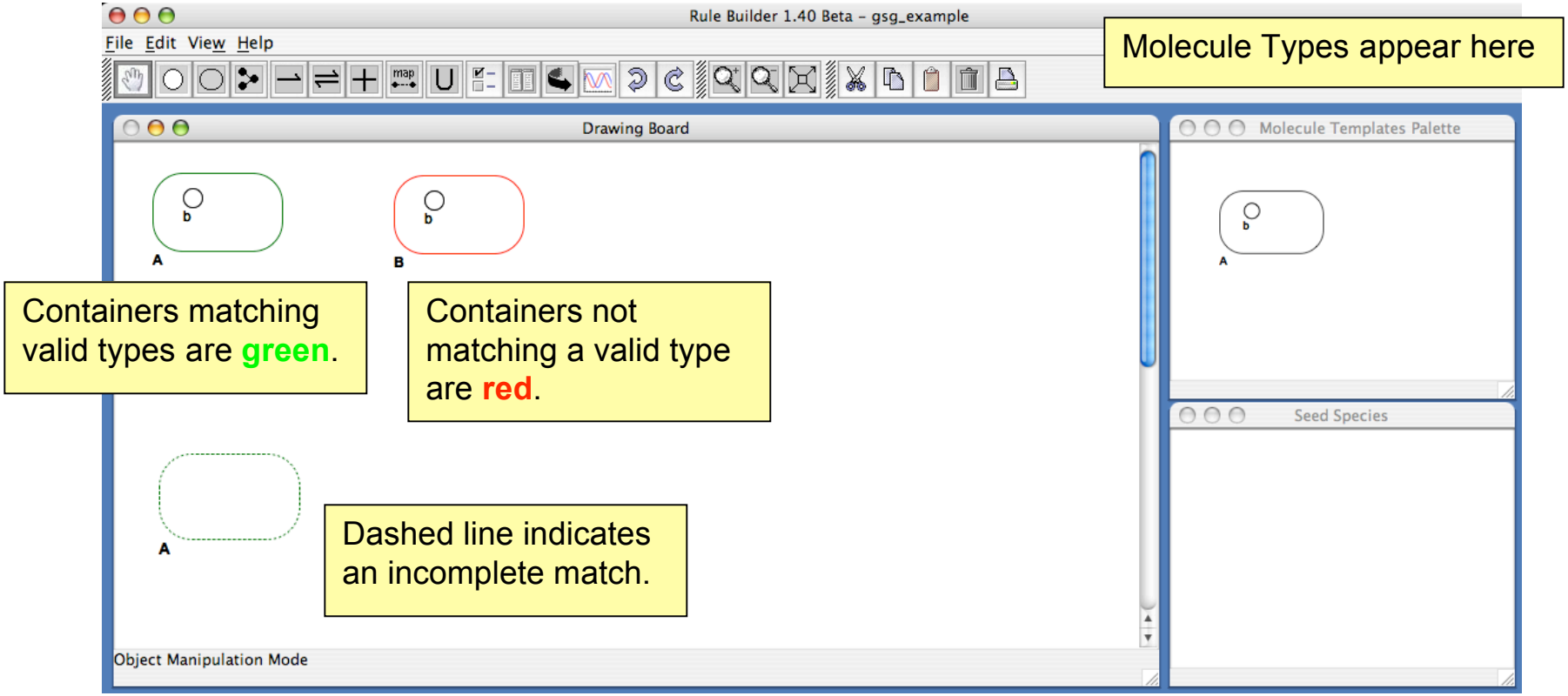
Setting Allowed Component States

Components may take on different states to indicate conformation or covalent modification, such as phosphorylation.

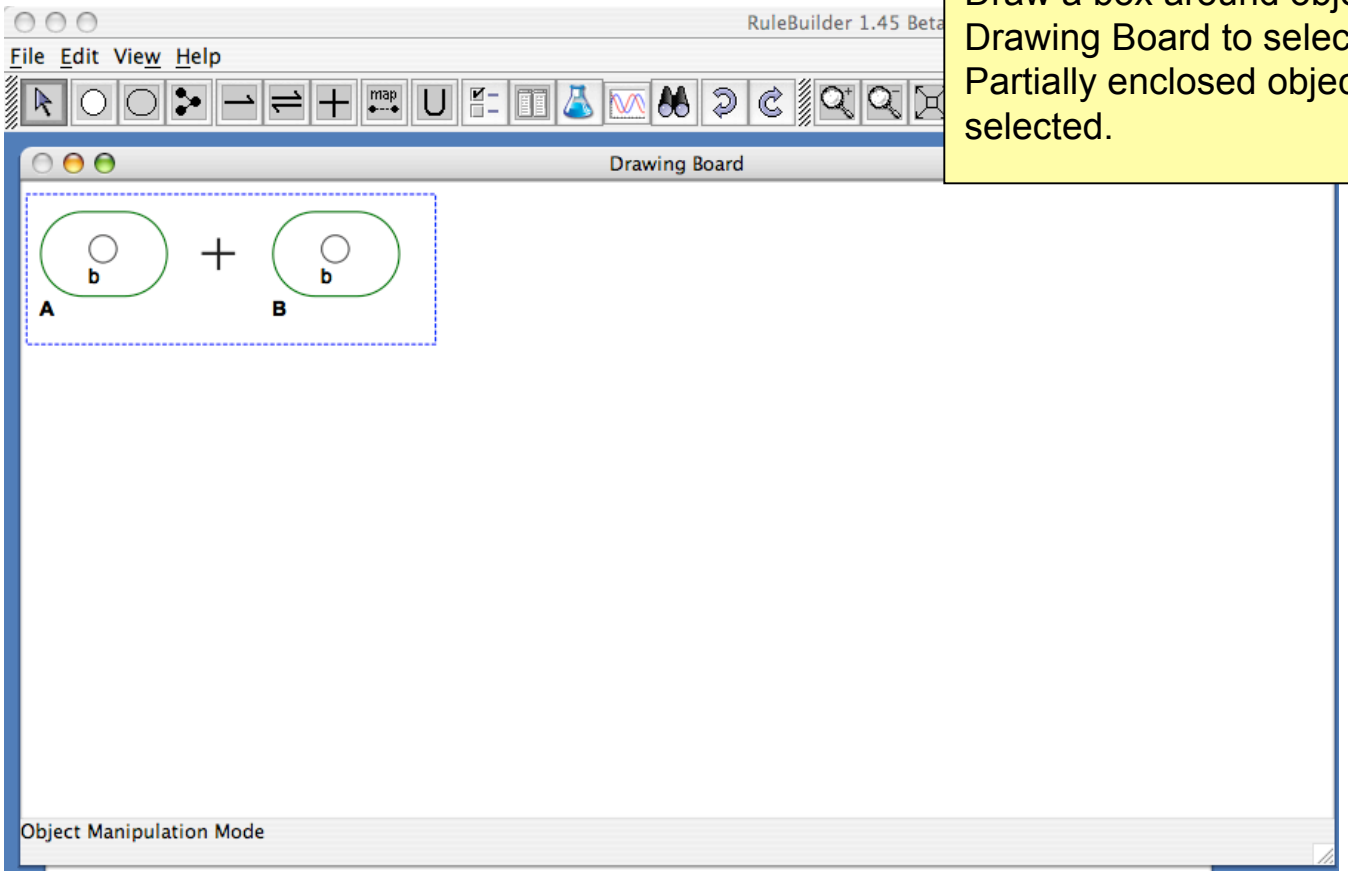


Selecting Create Molecule Type brings up the Component State dialog. Add an allowed state by typing in the Add Allowed State box and clicking Add. Components don't need to have any allowed states. Exit the dialog by clicking Done.

Identifying Valid and Invalid Molecules

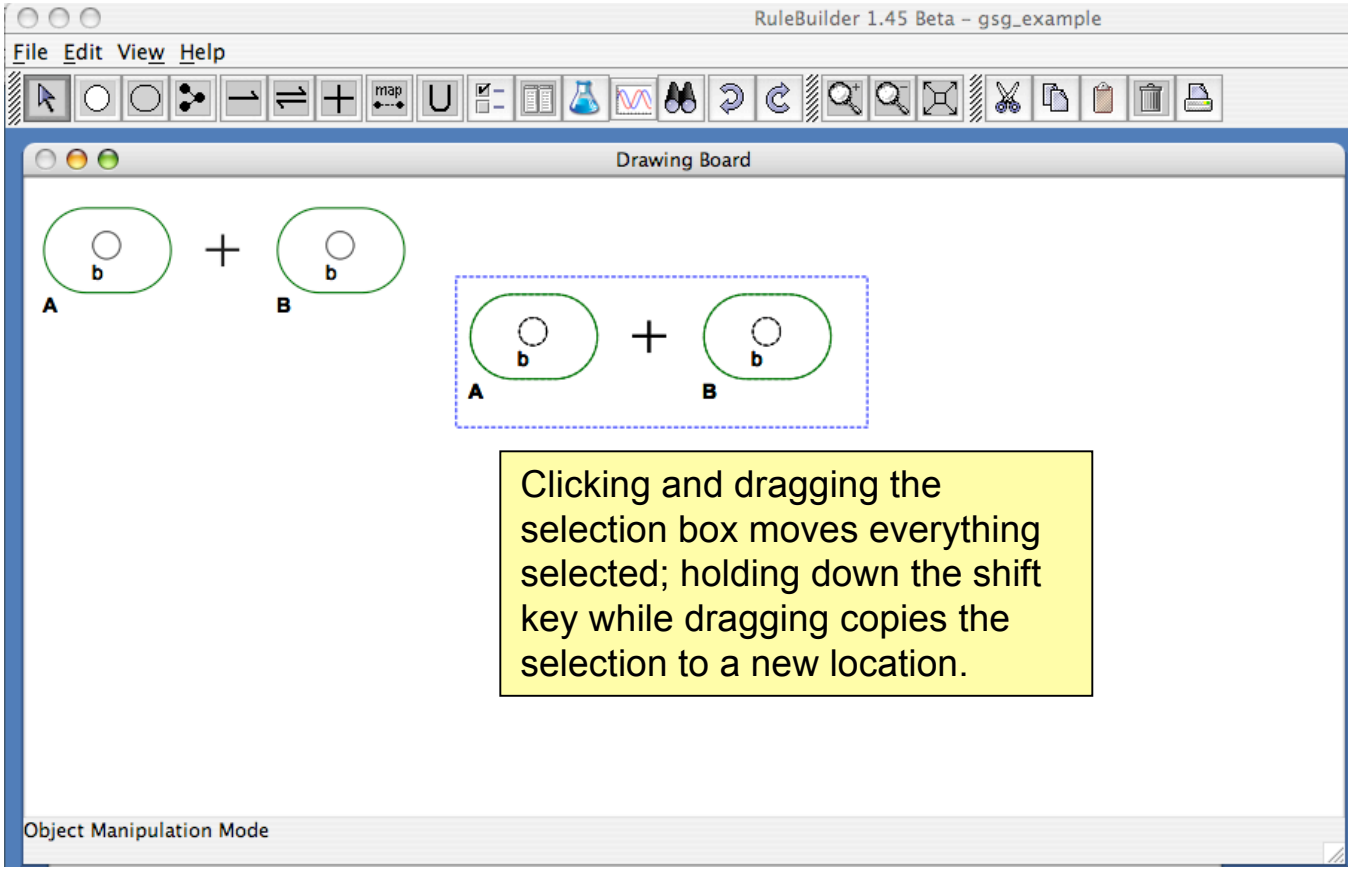


Copying Objects with the Selection Box



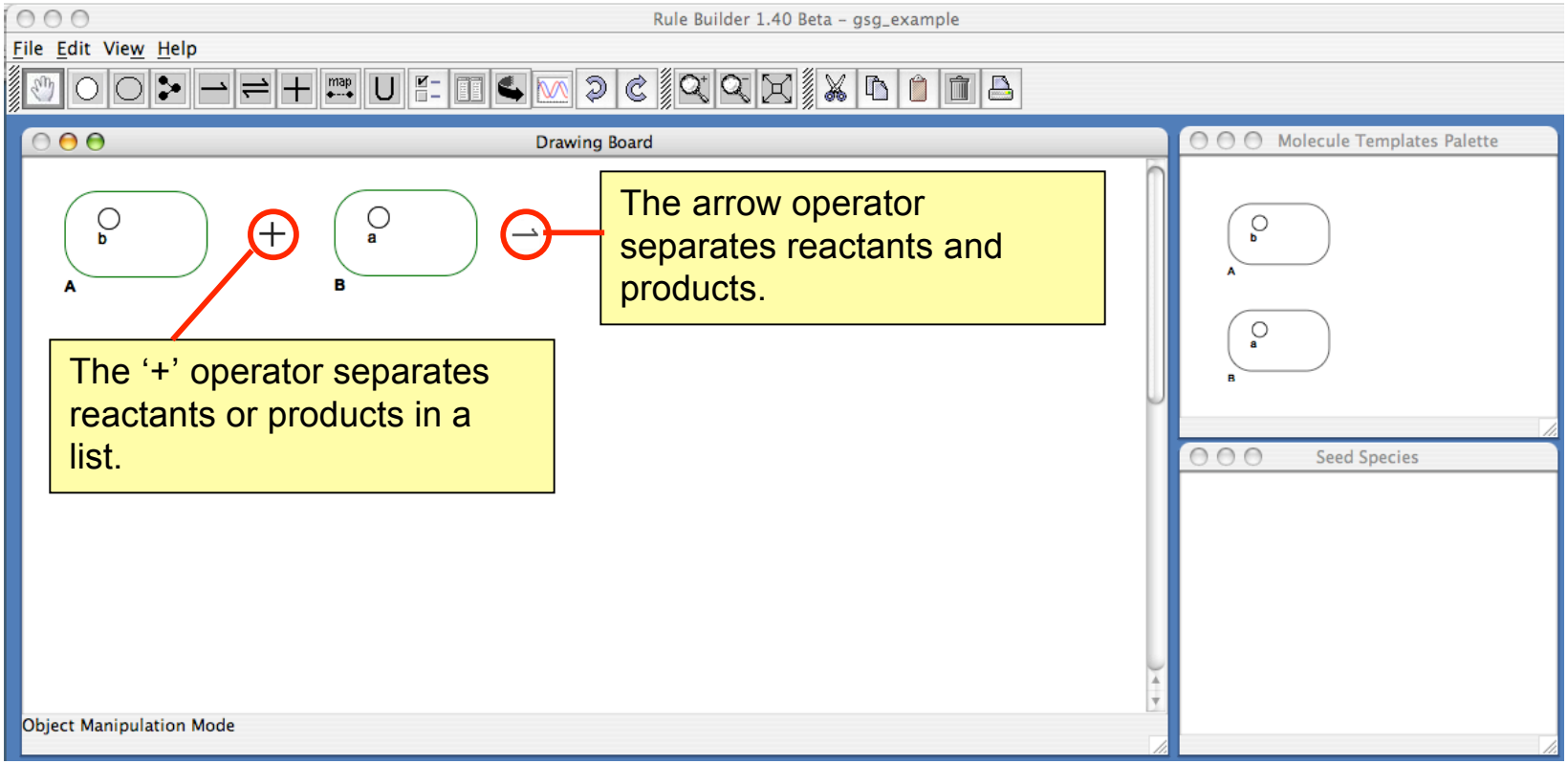
Draw a box around objects on the Drawing Board to select them. Partially enclosed objects are not selected.

Copying Objects with the Selection Box



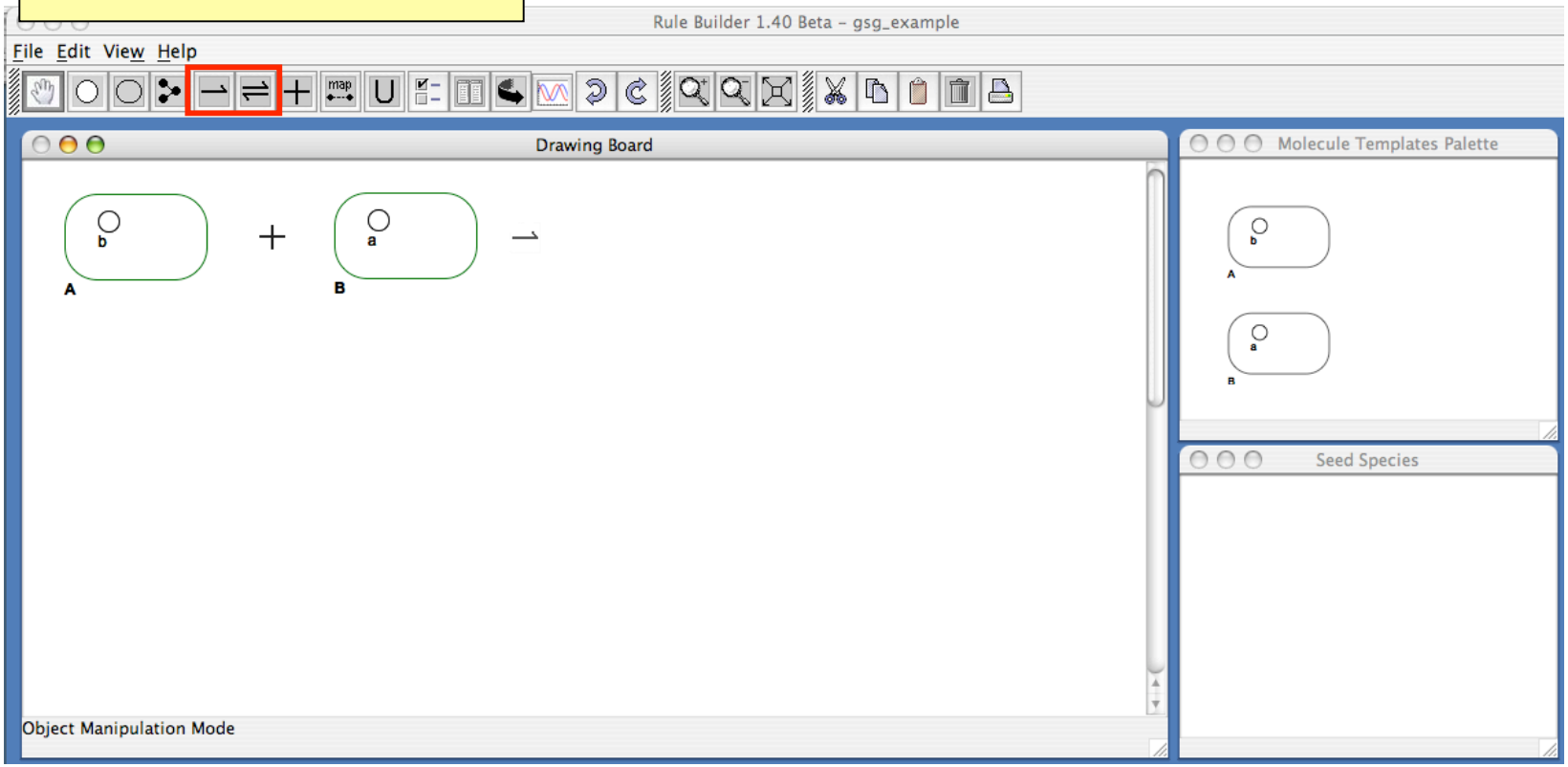
Creating a Reaction Rule

Reaction rules are created by arranging containers and operators to construct a formula for the reaction.

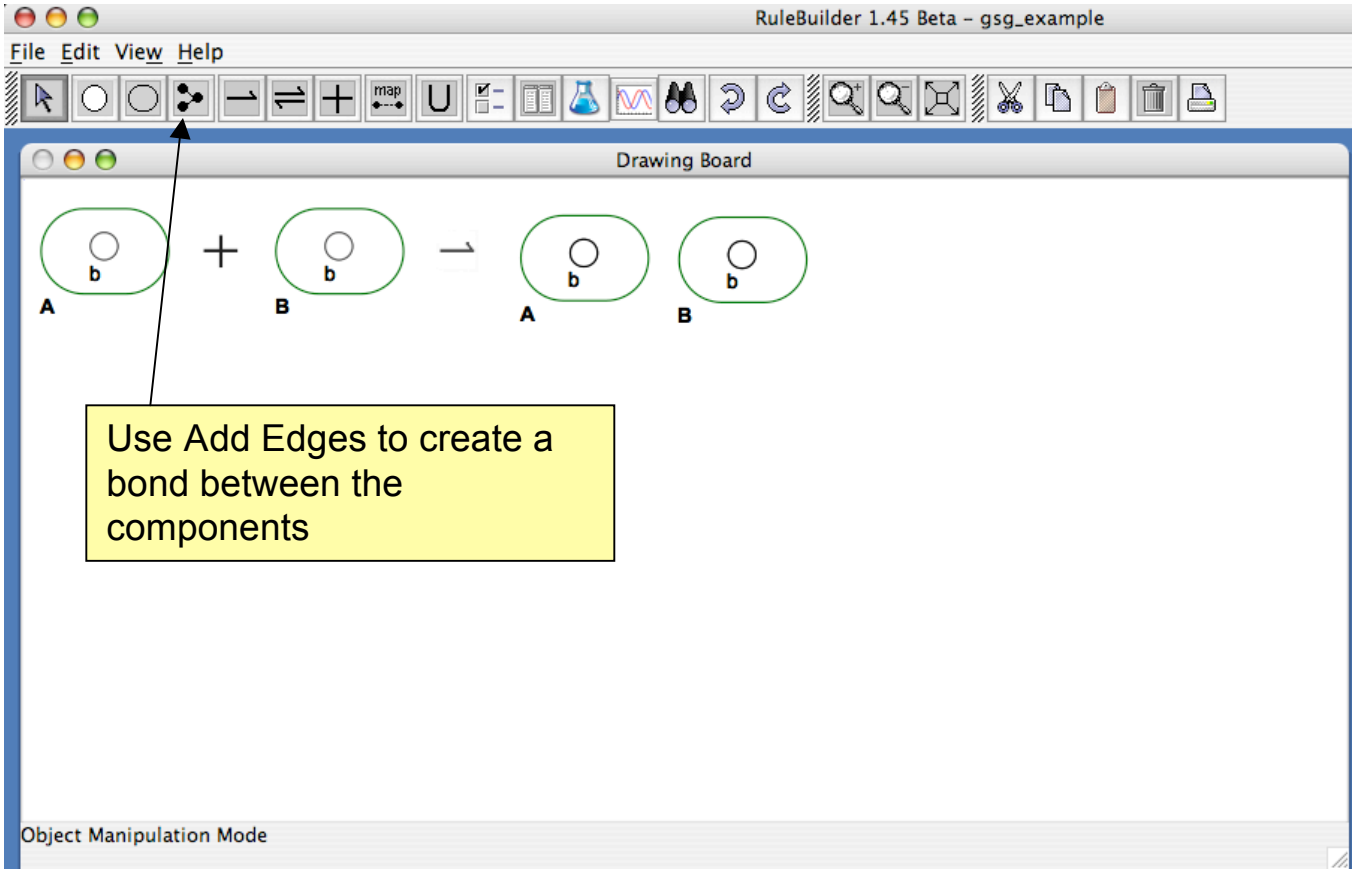


Creating a Reaction Rule

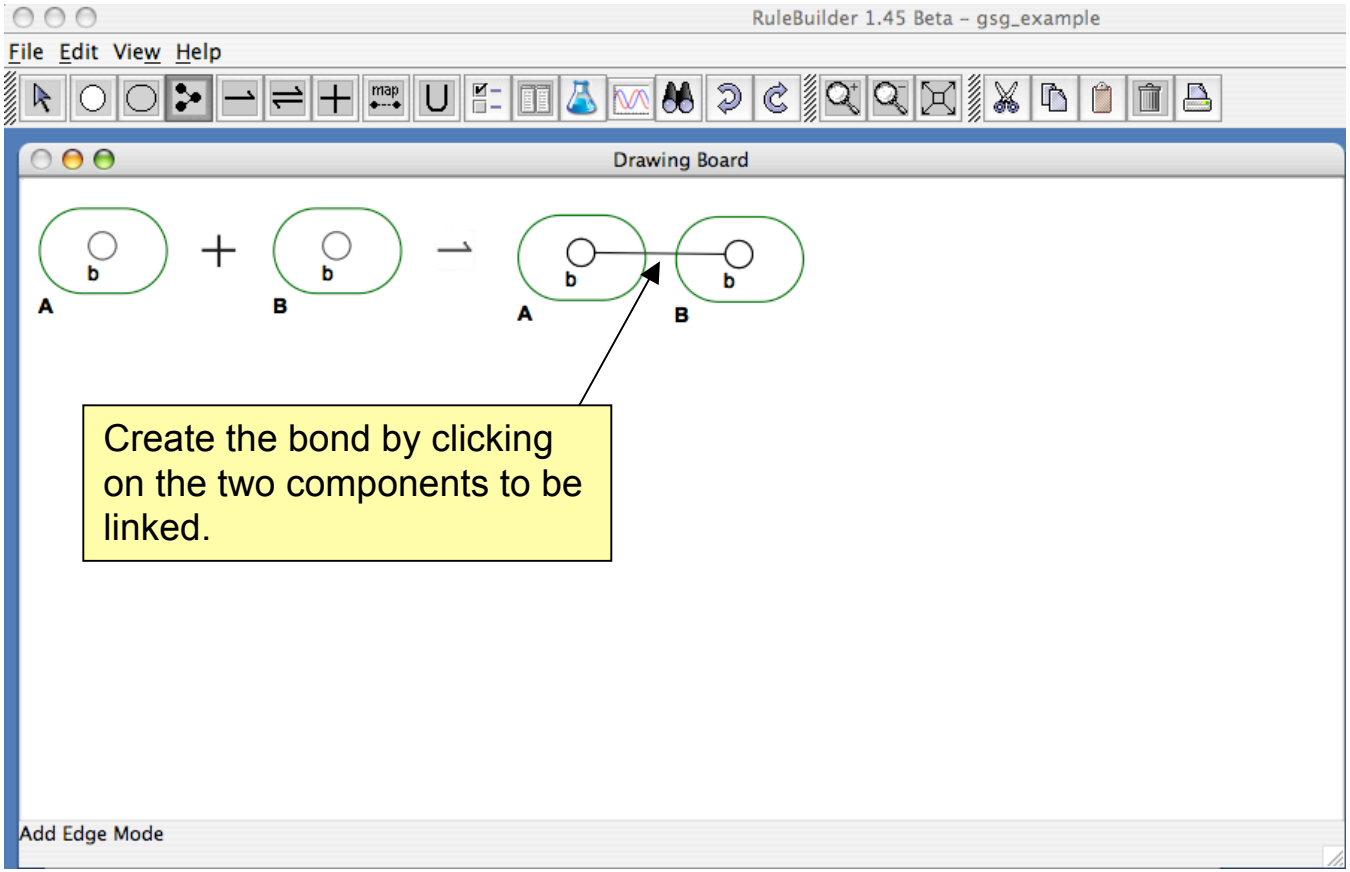
The type of arrow determines whether a reaction is reversible or irreversible.



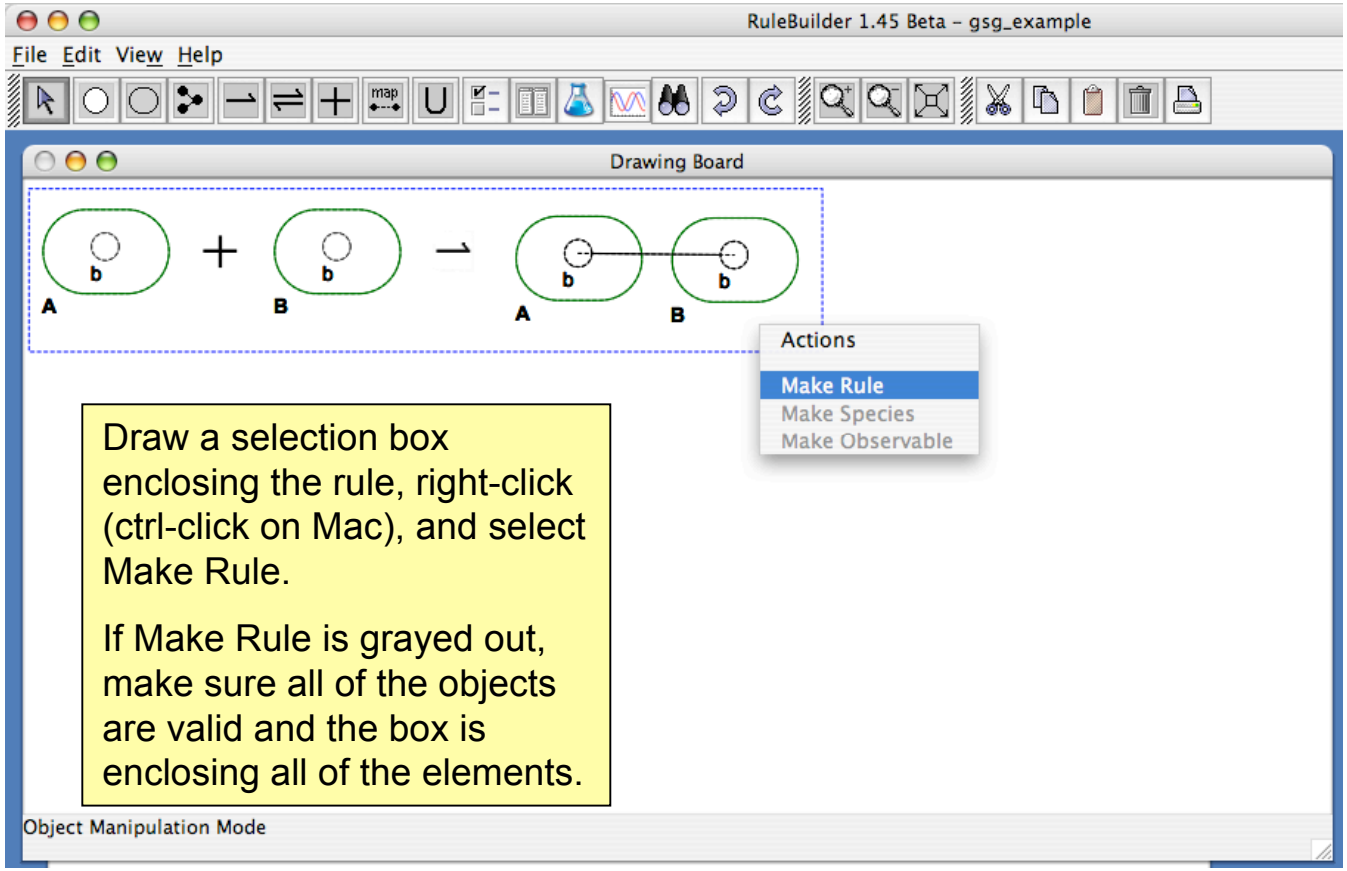
Defining Products



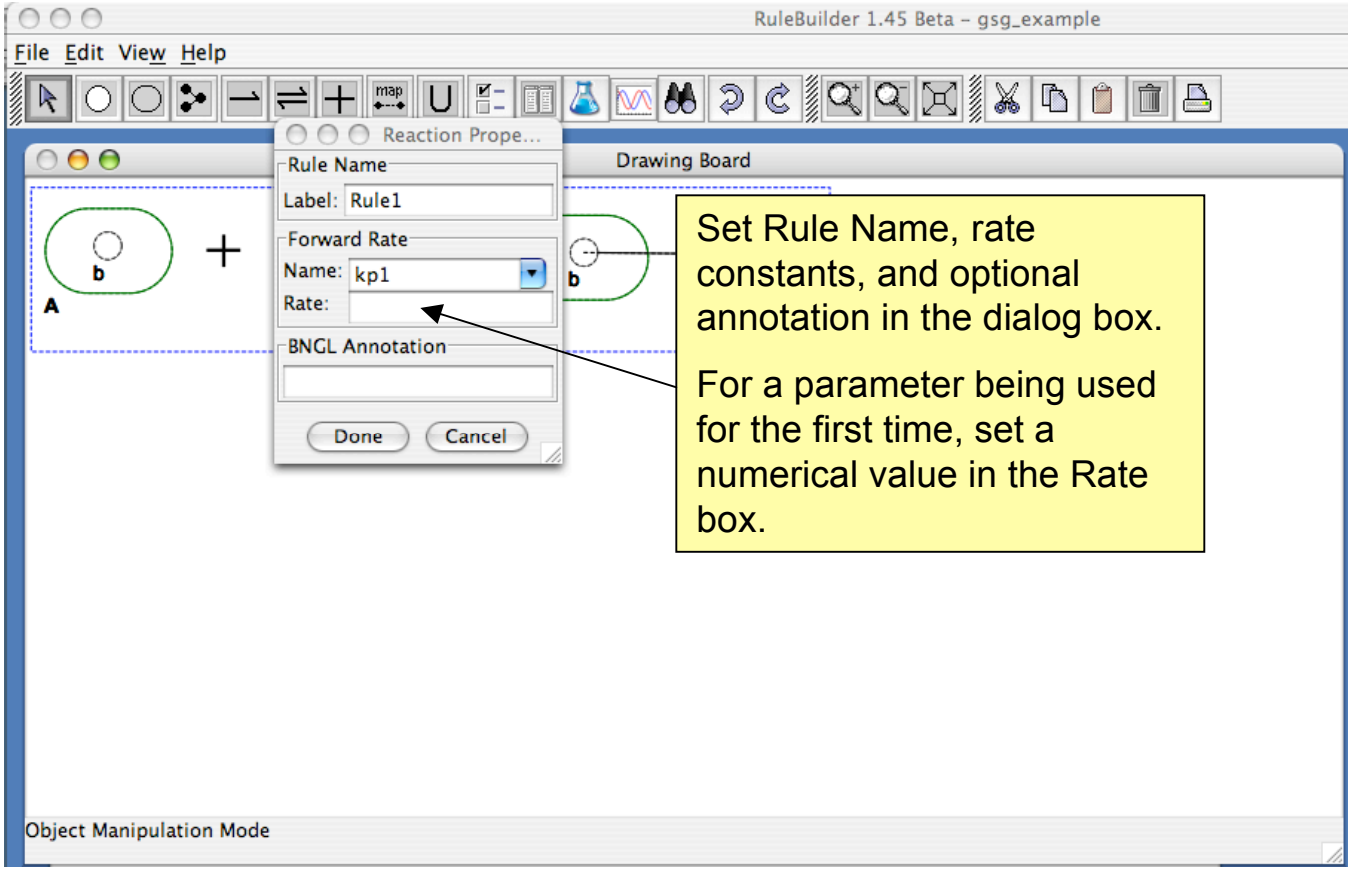
Defining Products



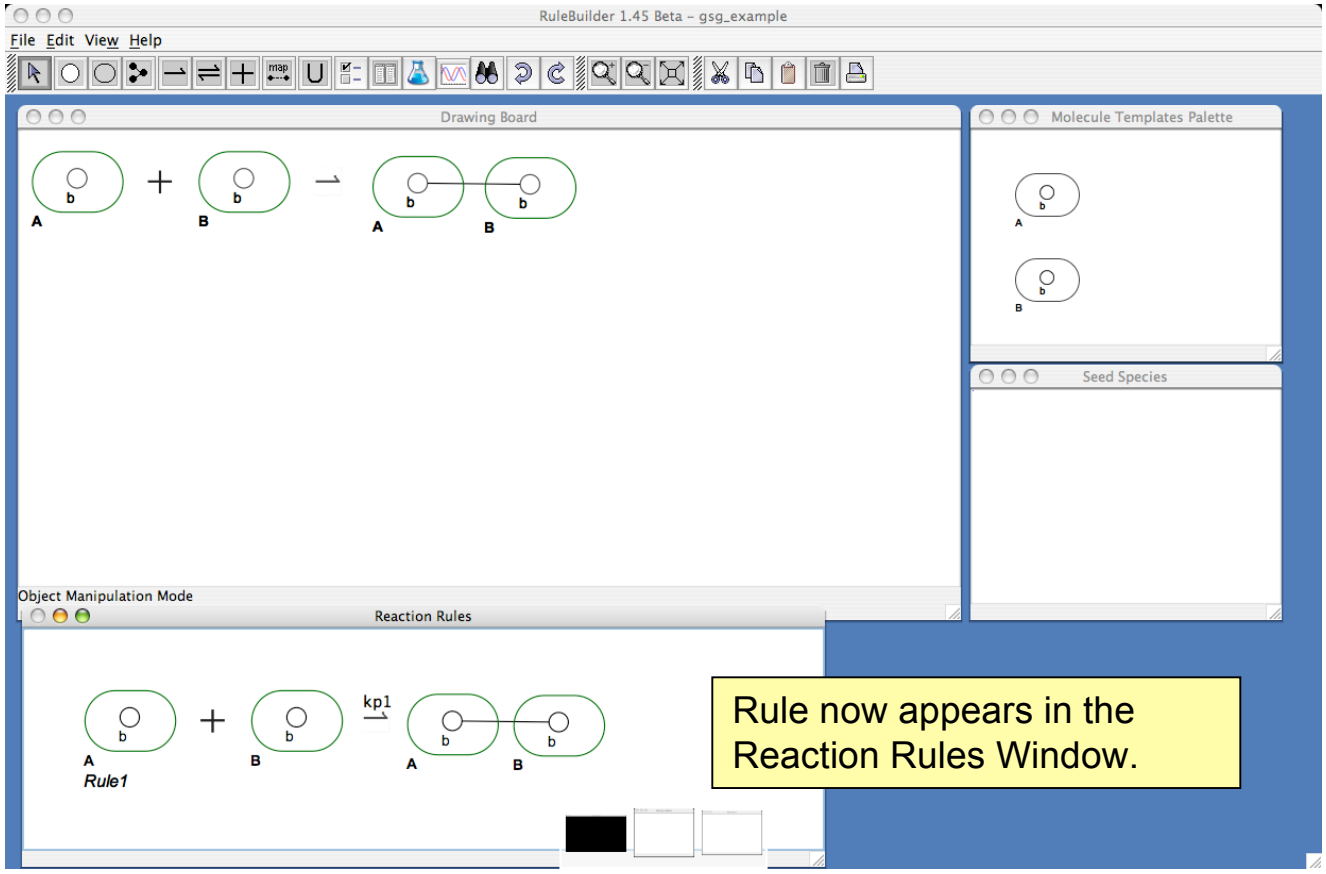
Creating the Rule



Make Rule Dialog

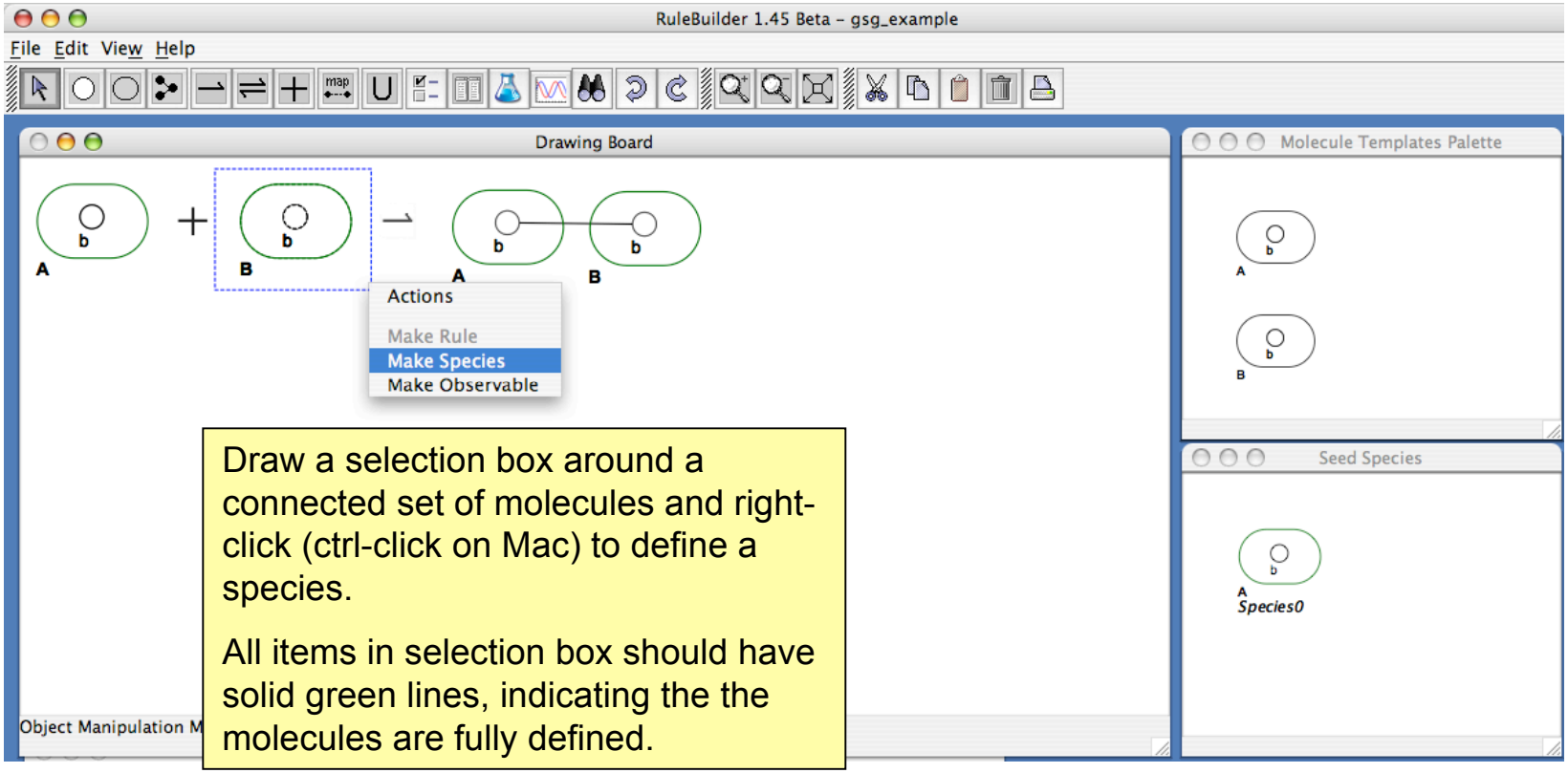


Reaction Rules Window



Defining Seed Species

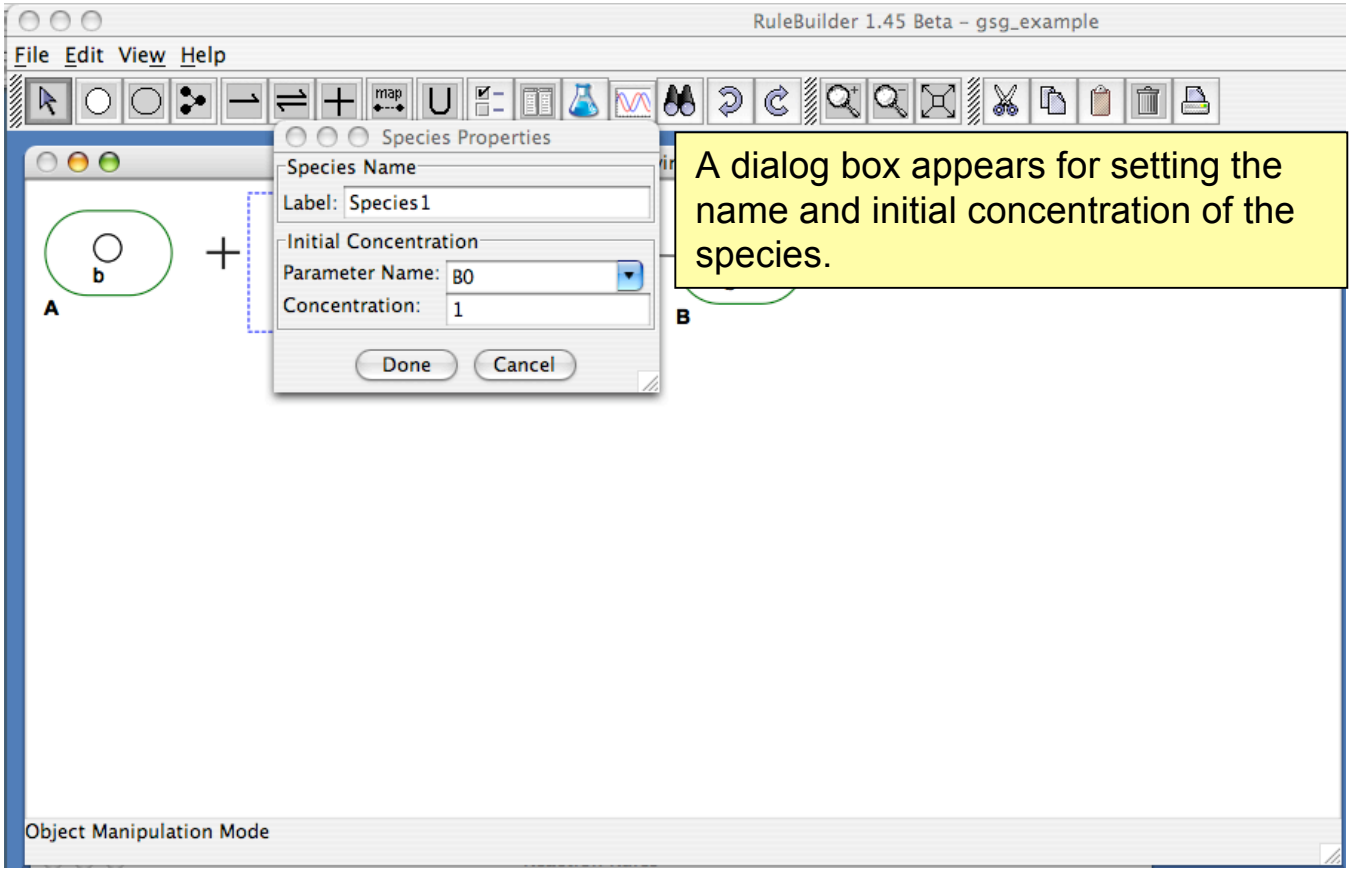
The network is defined by applying the reaction rules to a set of seed species.



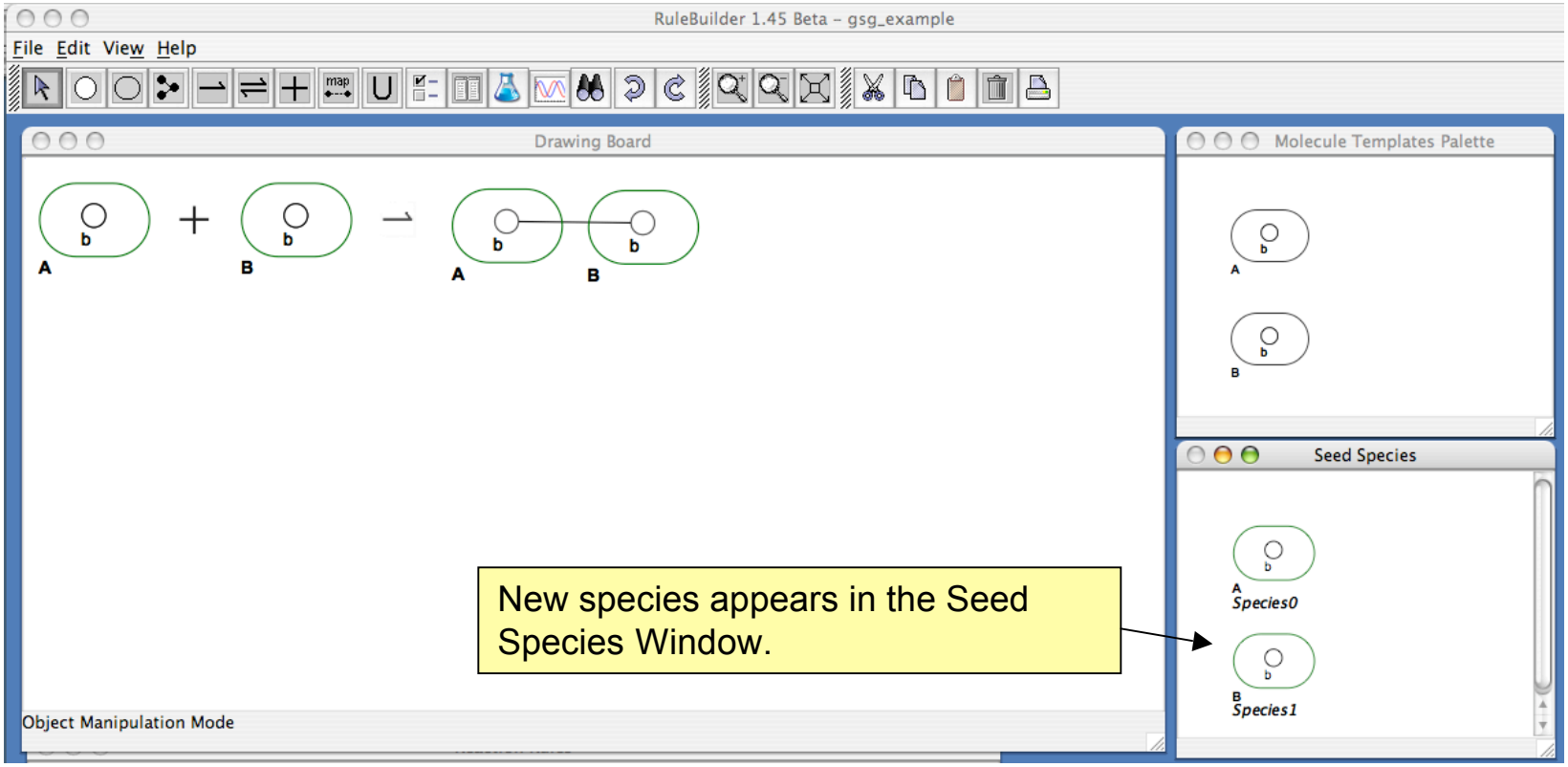
Draw a selection box around a connected set of molecules and right-click (ctrl-click on Mac) to define a species.

All items in selection box should have solid green lines, indicating the the molecules are fully defined.

Species Dialog Box

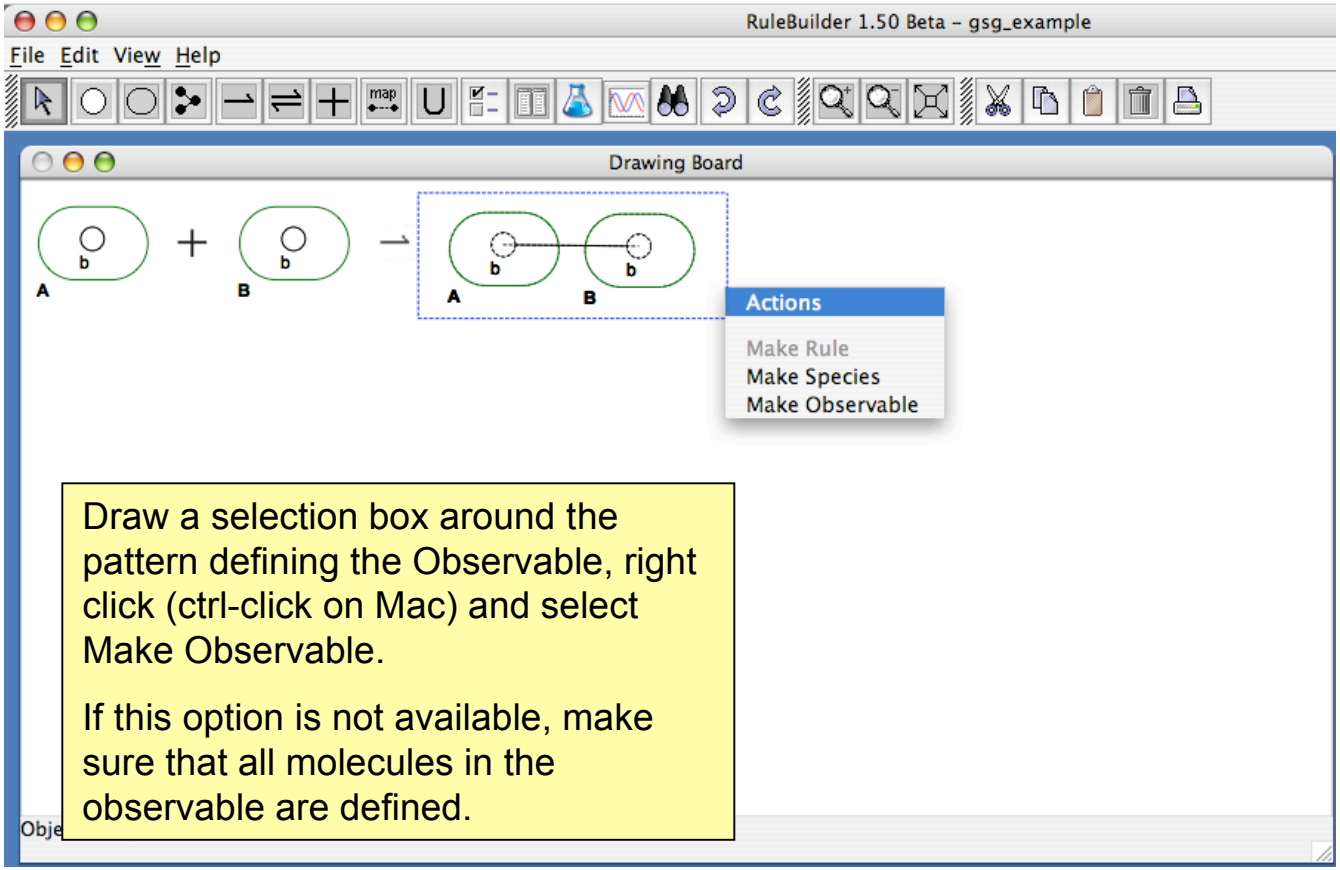


Seed Species Window

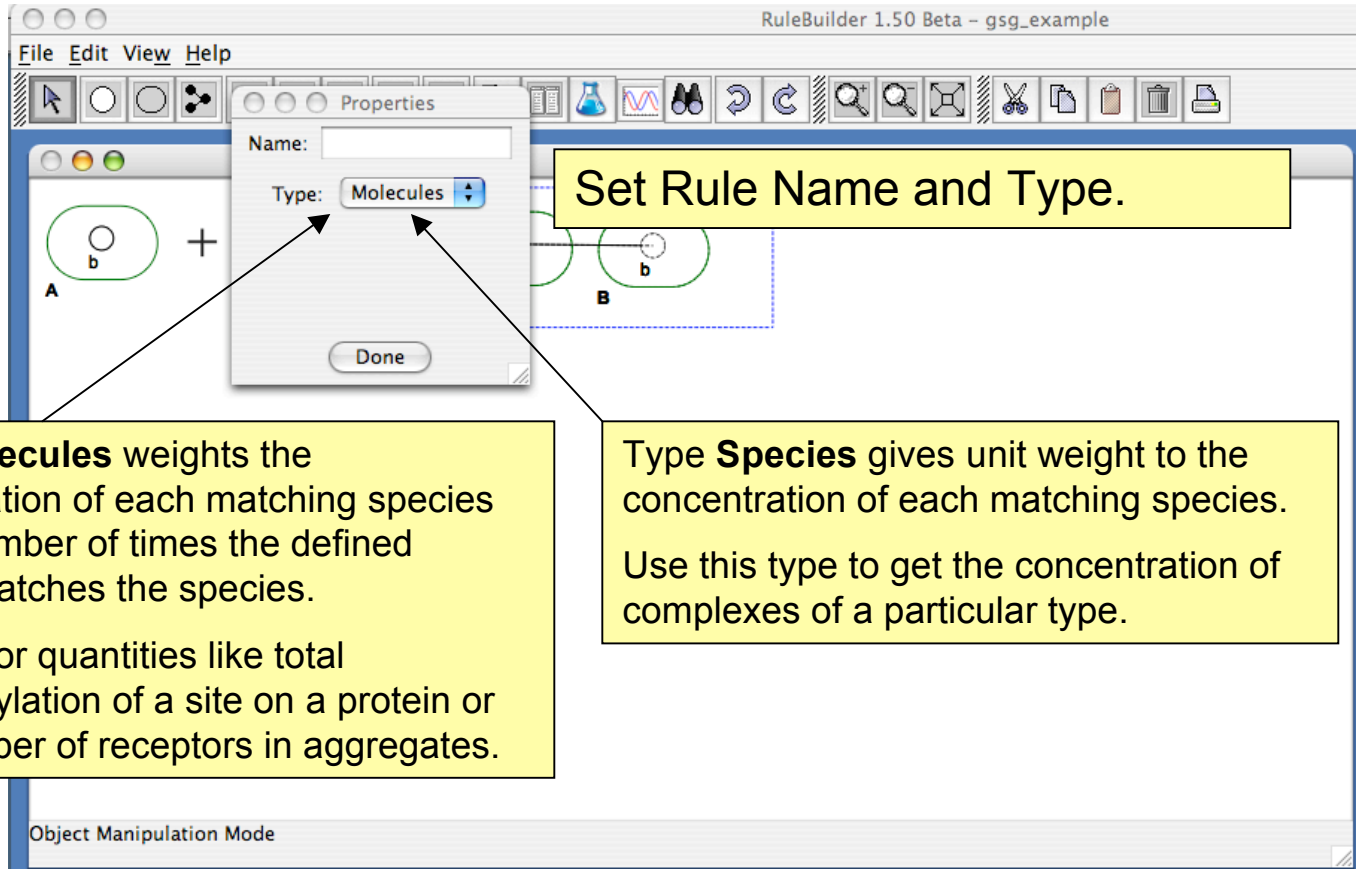


Defining Observables

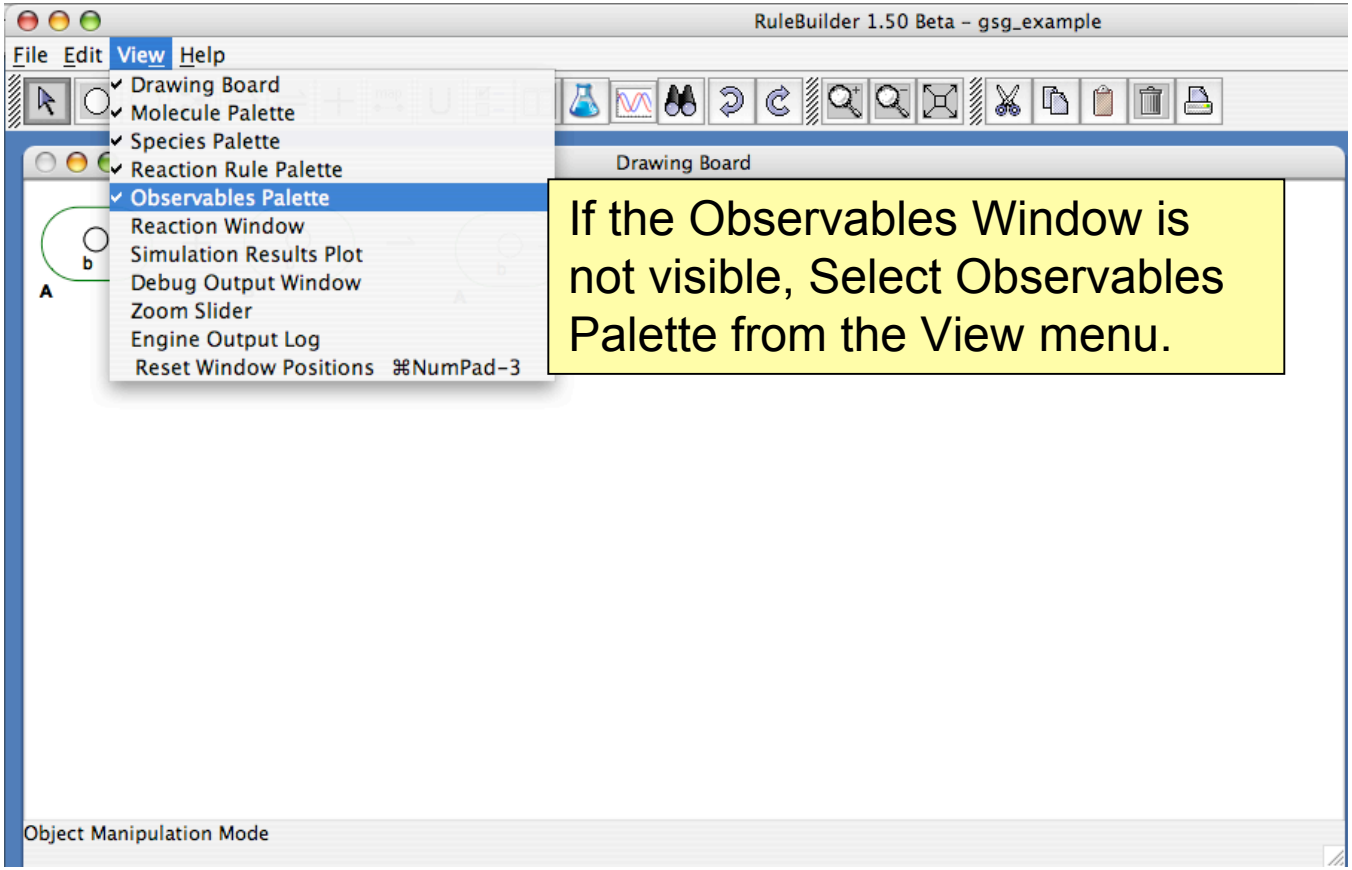
Observables are concentration sums over species with particular properties and correspond to model outputs, such as total phosphorylation of a protein.



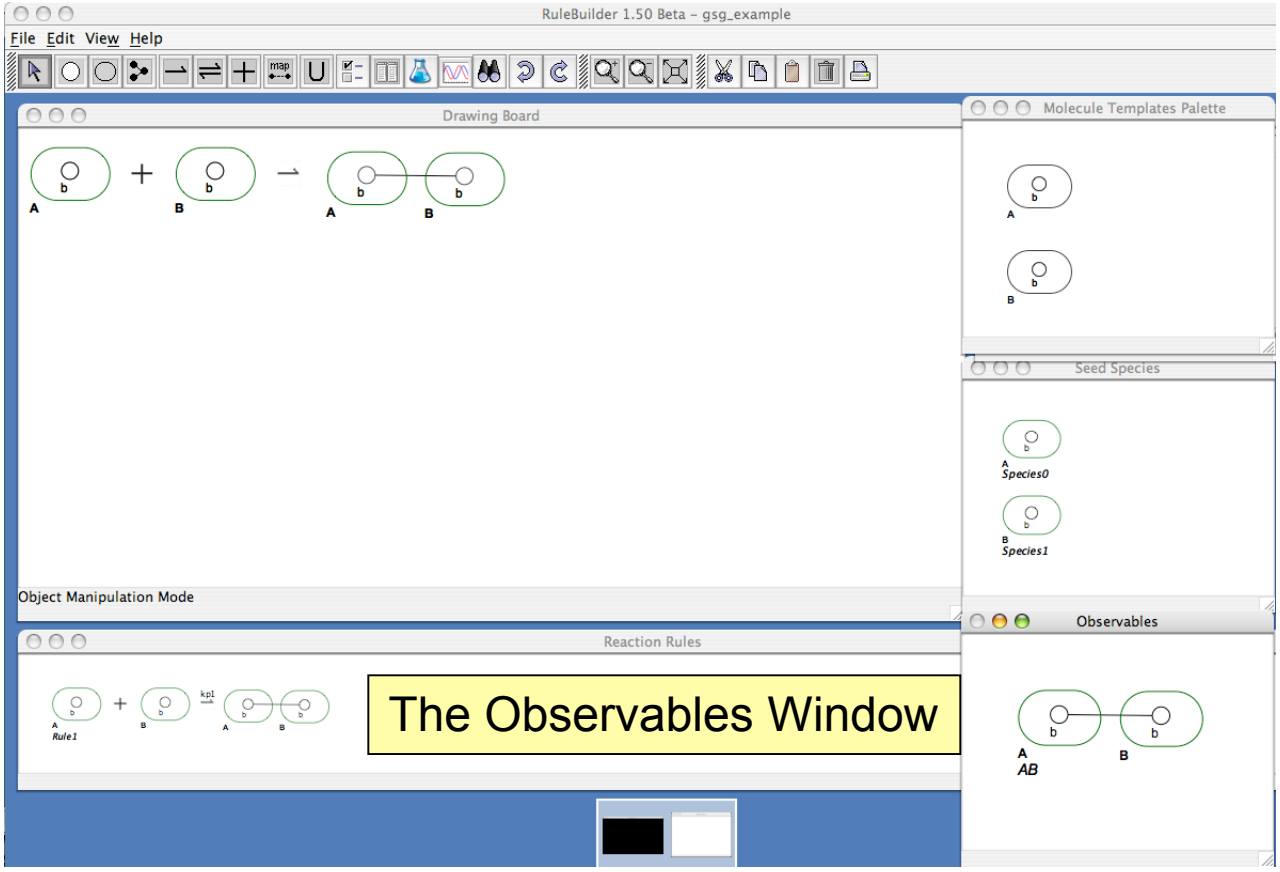
Make Observables Dialog



Observables Window

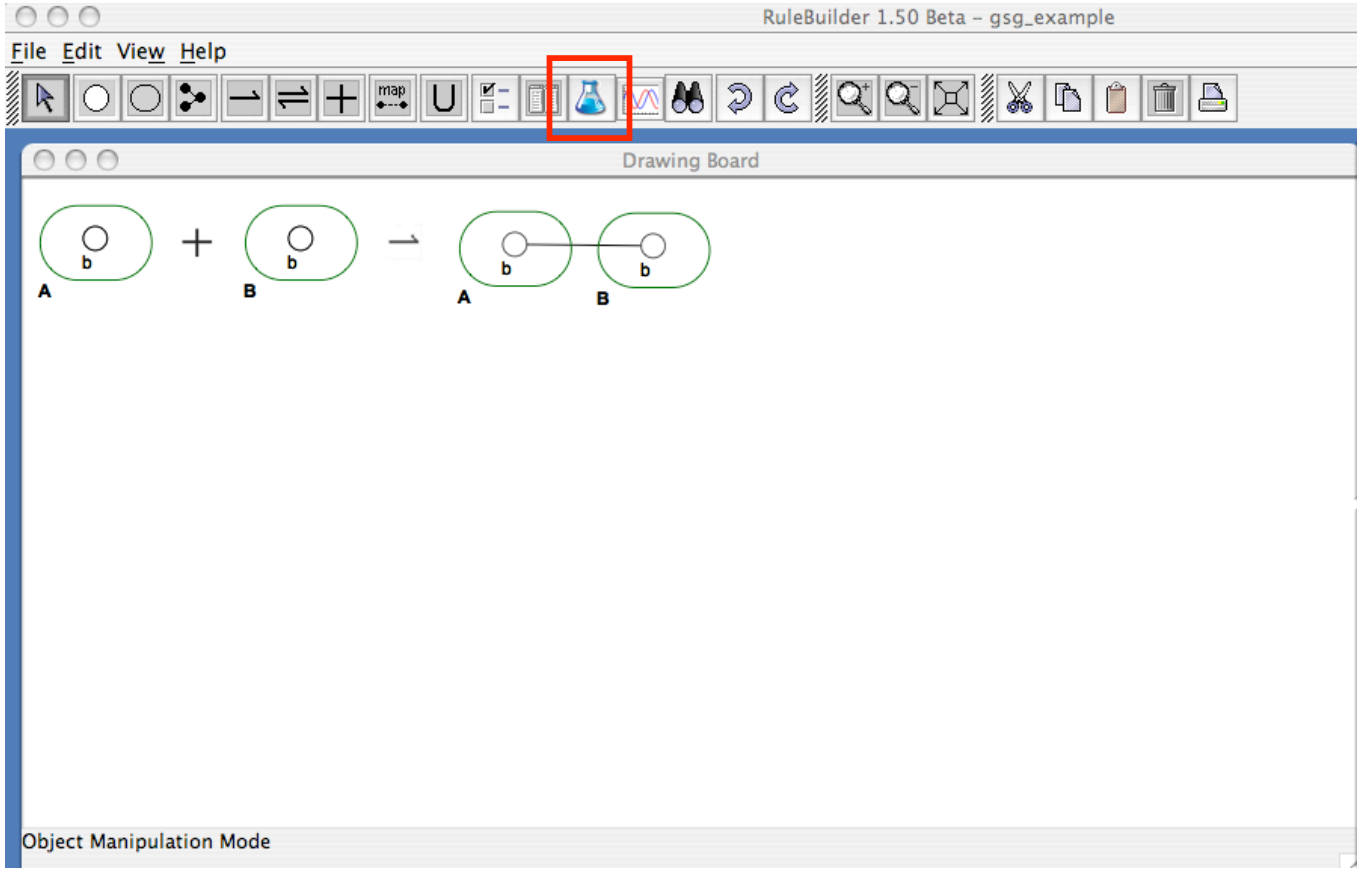


Observables Window

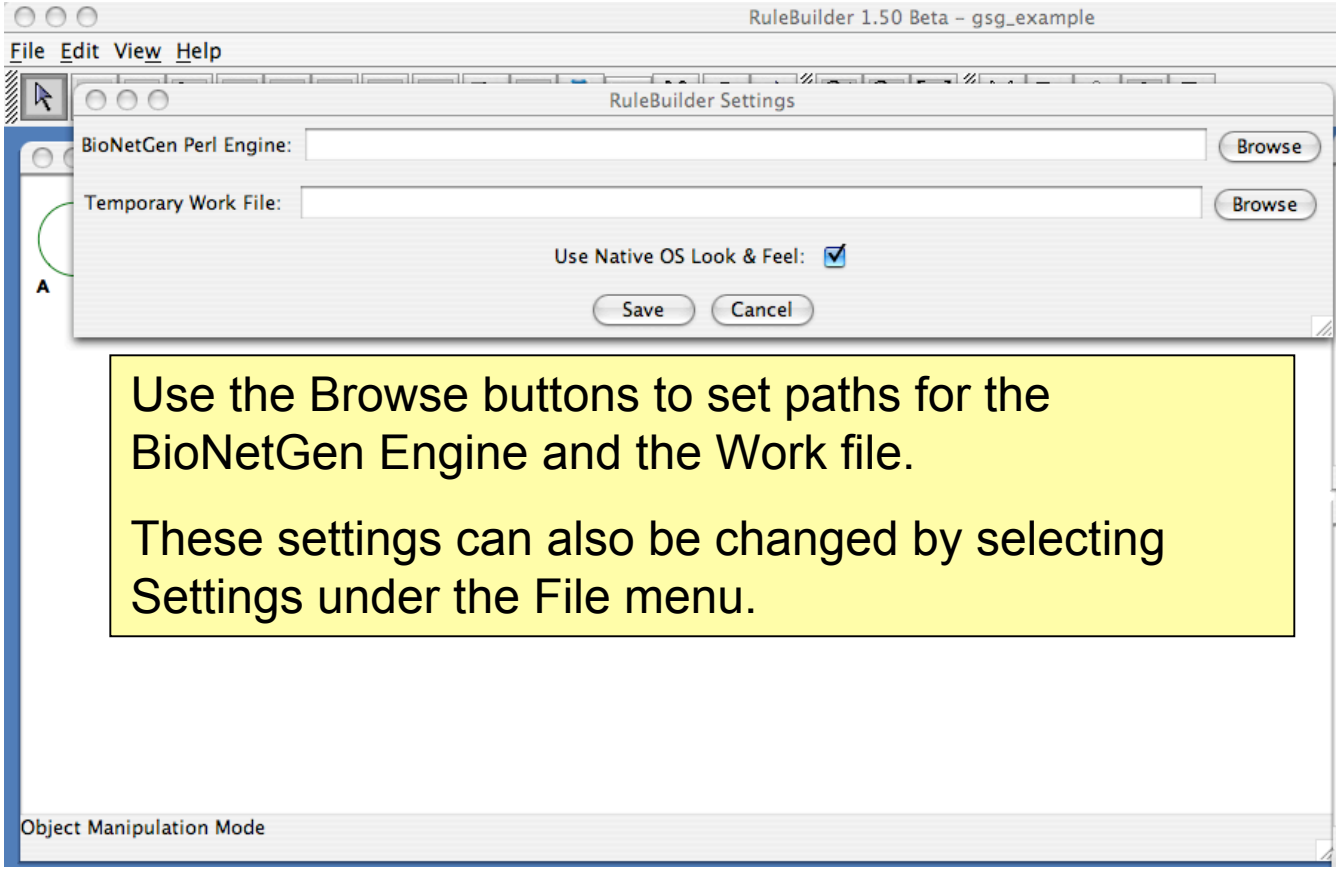


Running the Model

Once Reaction Rules, Seed Species, and Observables (optional) have been defined, the model can be simulated by pressing Run BioNetGen button.

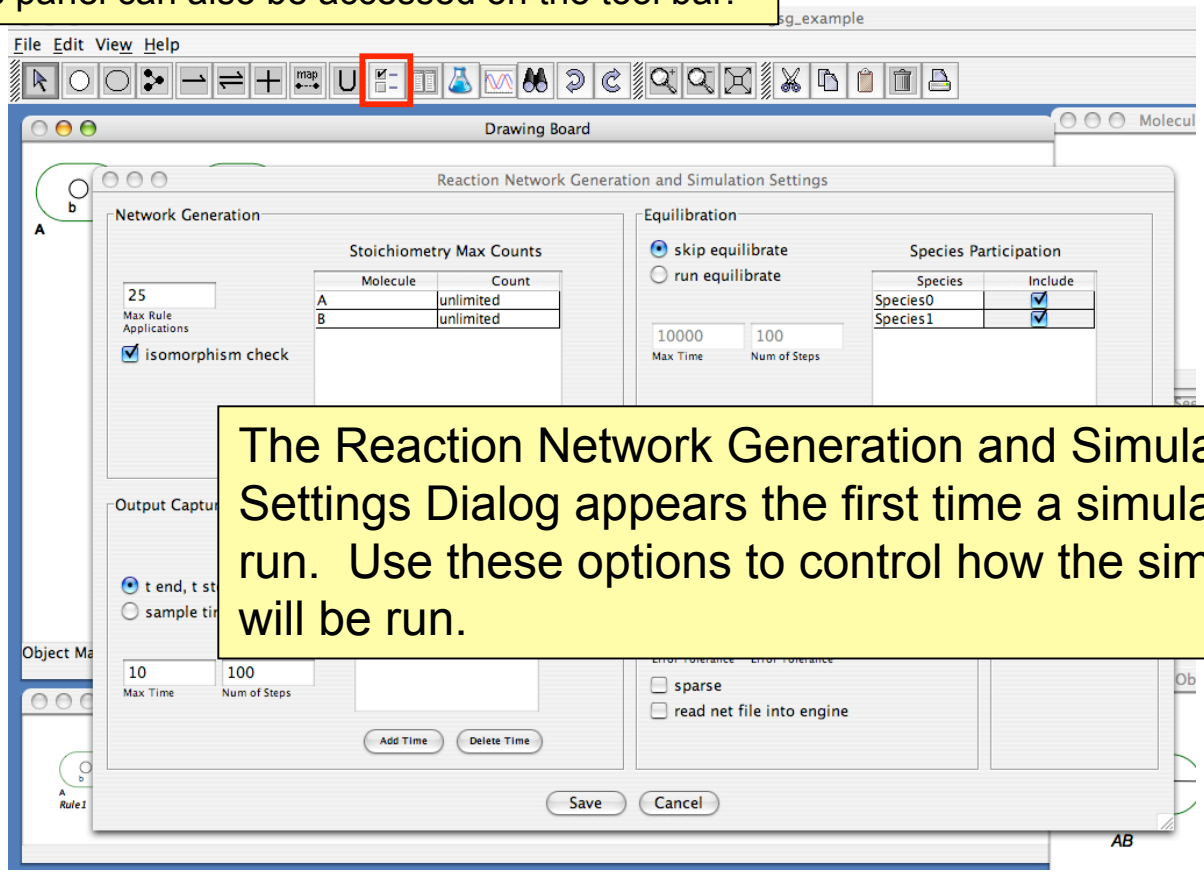


BioNetGen Engine Settings



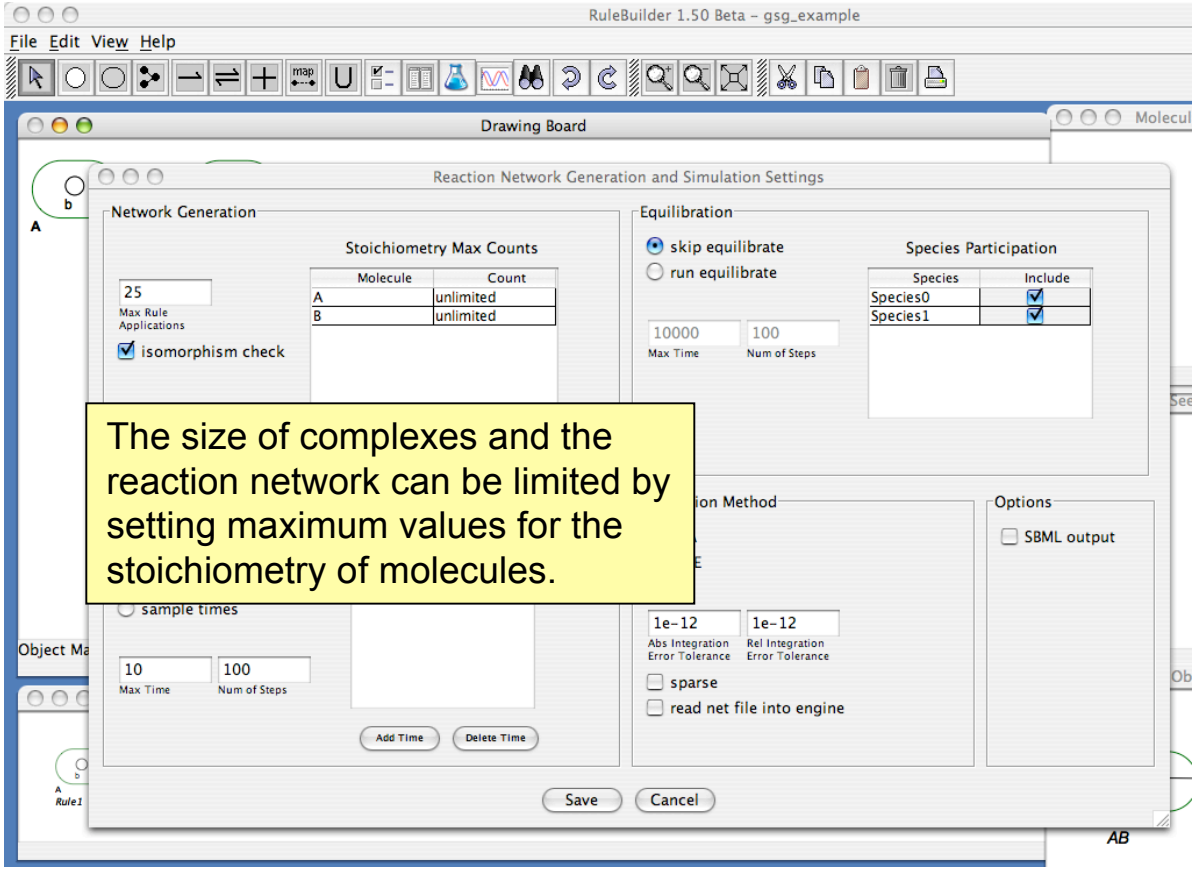
The SimConfig Panel

This panel can also be accessed on the tool bar.

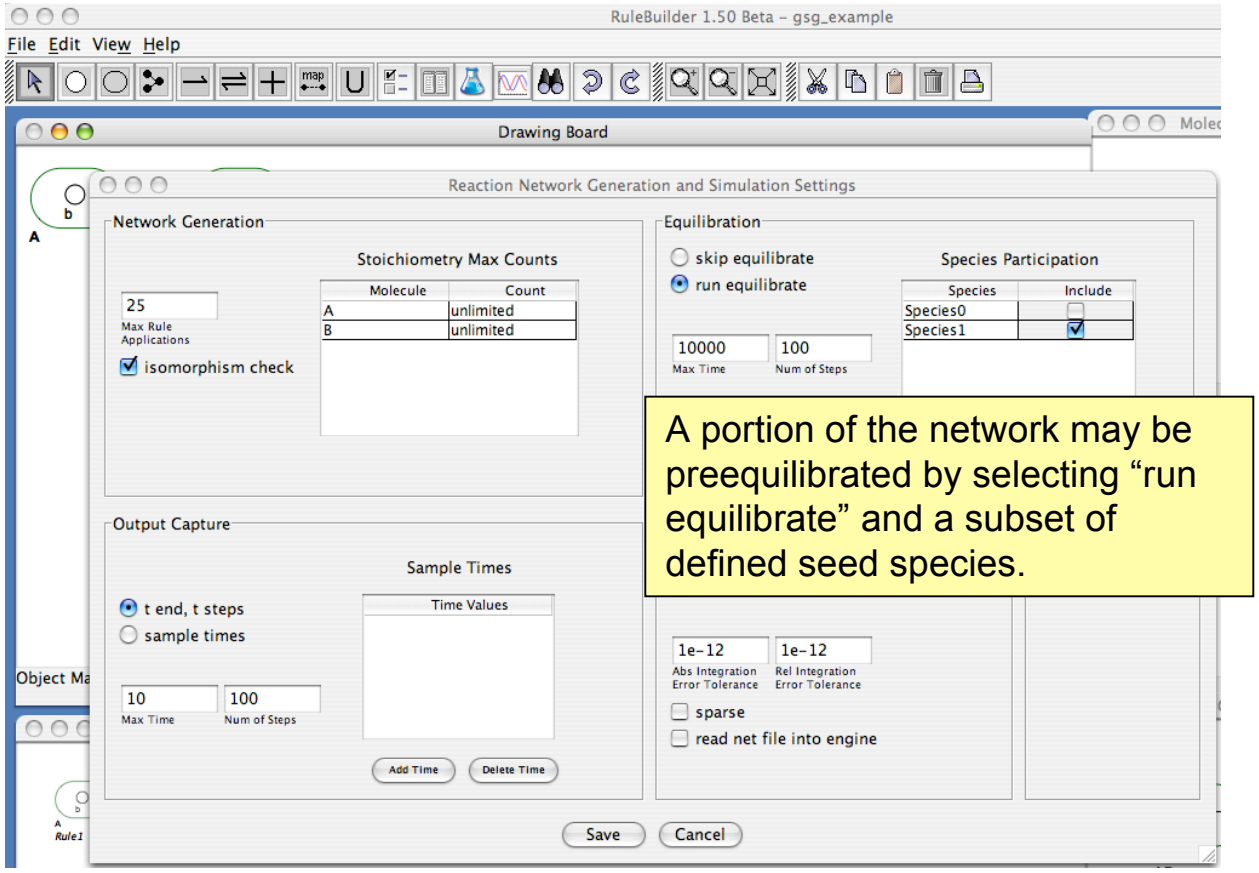


The Reaction Network Generation and Simulation Settings Dialog appears the first time a simulation is run. Use these options to control how the simulation will be run.

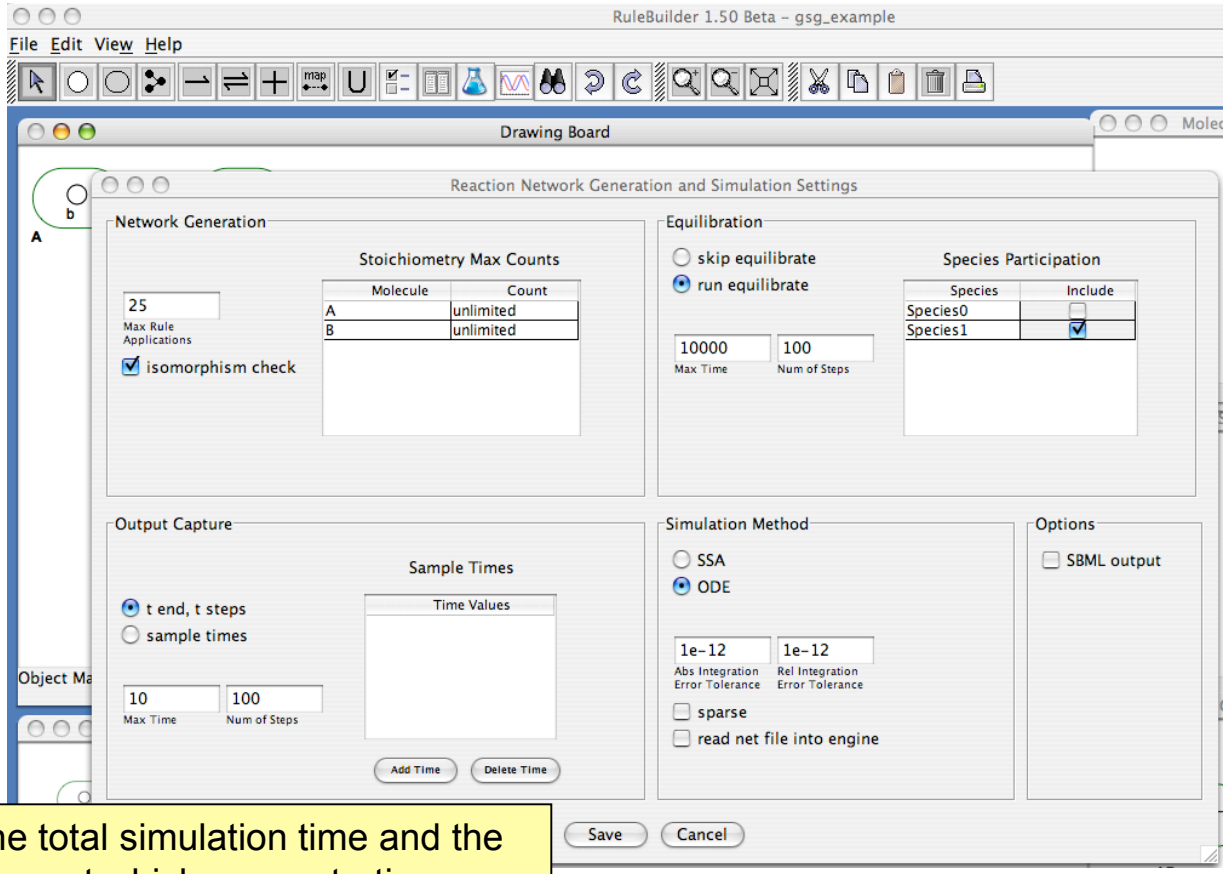
The SimConfig Panel



The SimConfig Panel

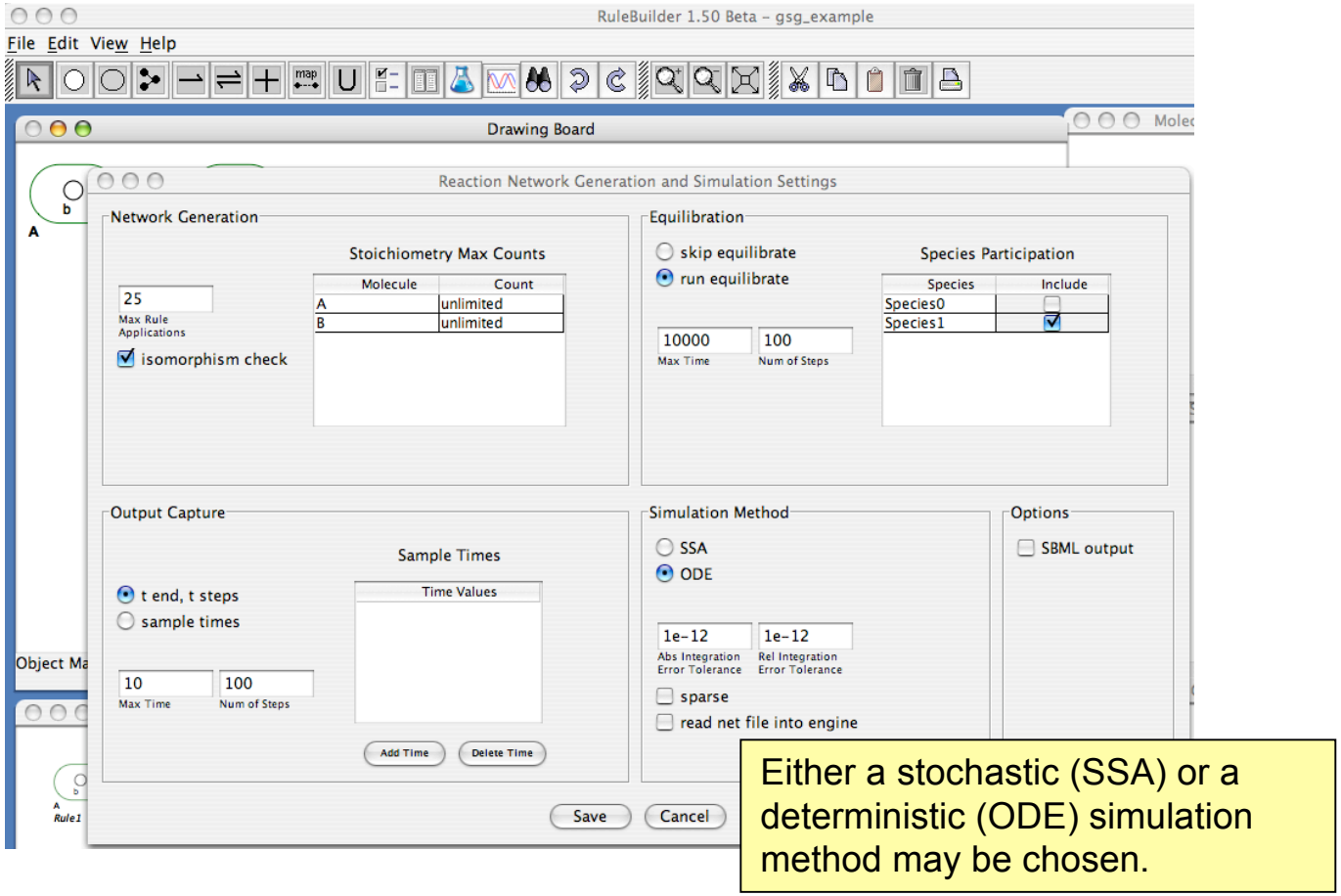


The SimConfig Panel

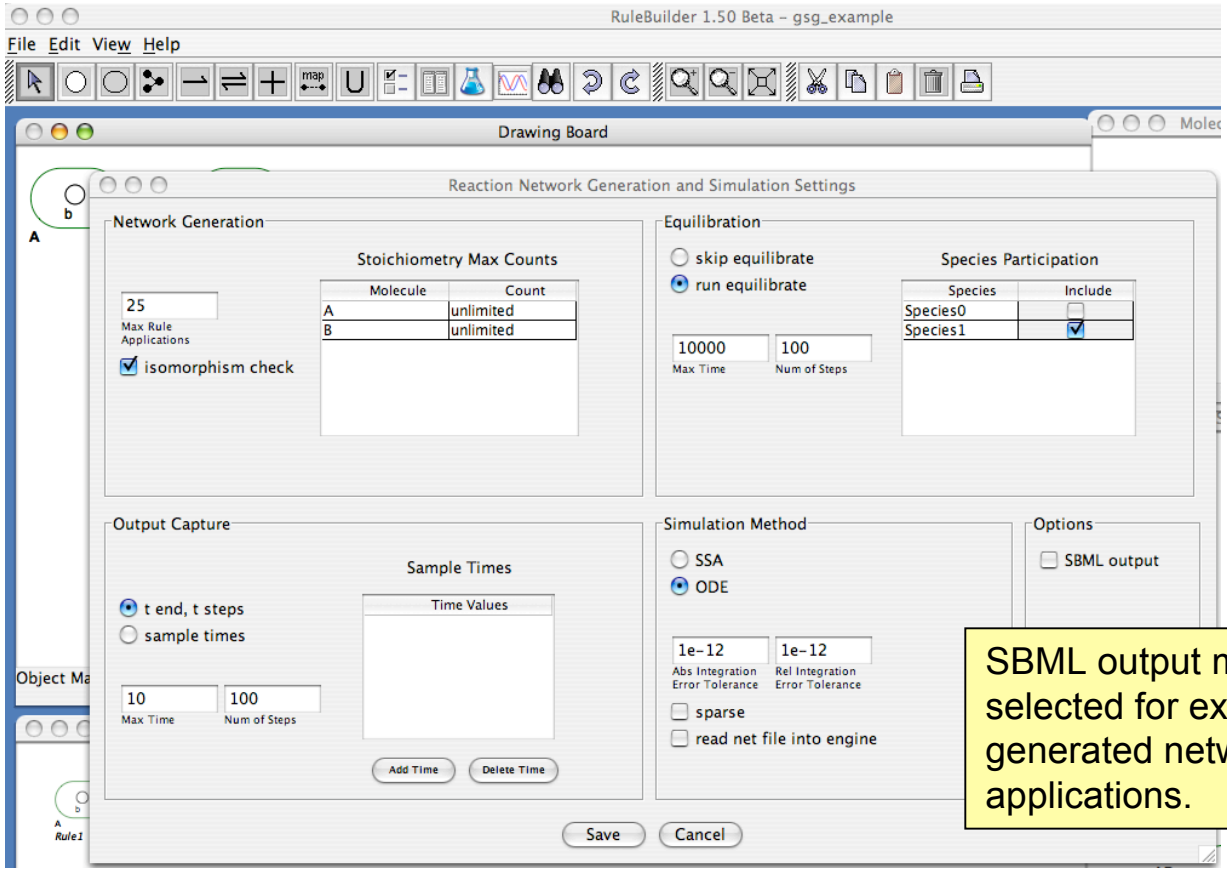


The total simulation time and the times at which concentrations are sampled are set here.

The SimConfig Panel

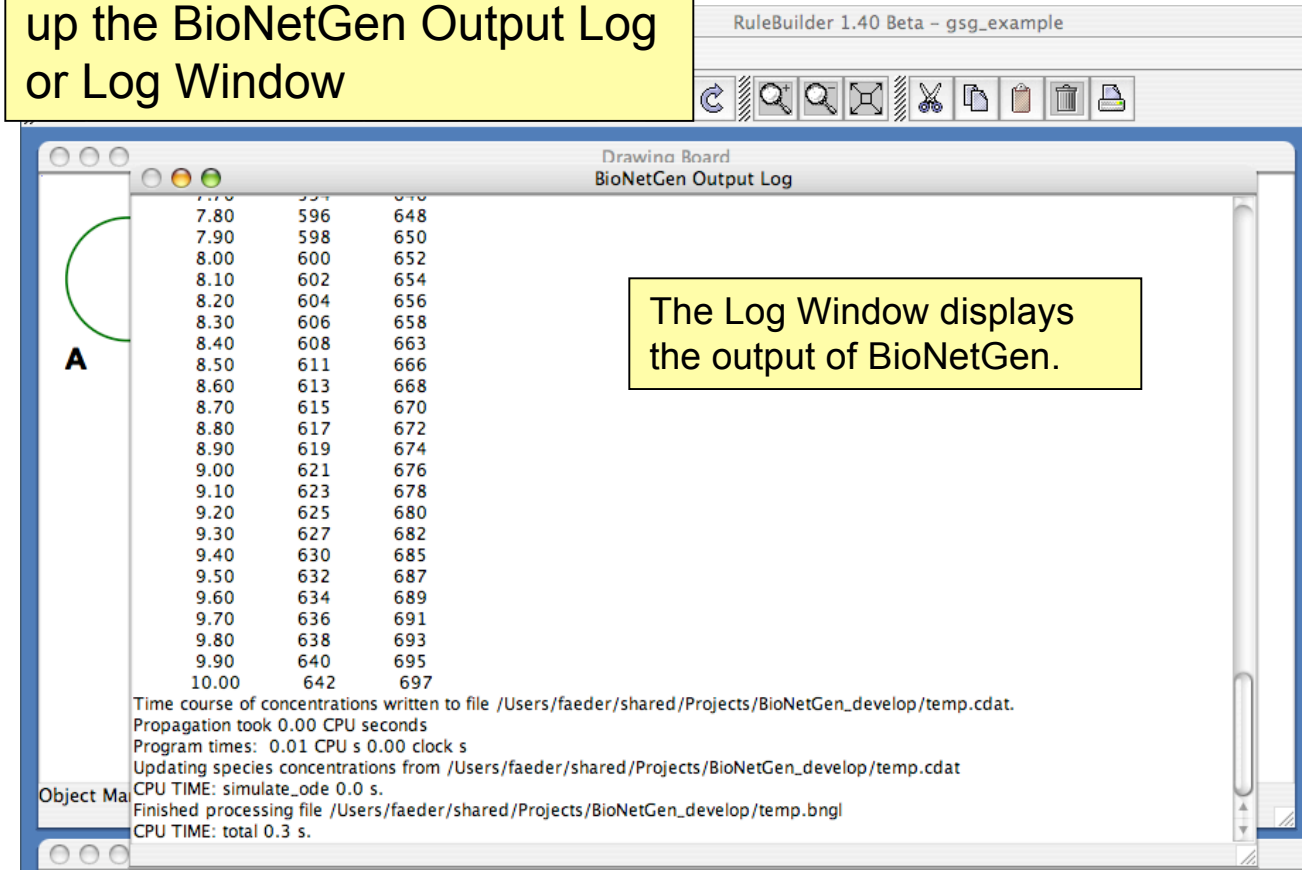


The SimConfig Panel



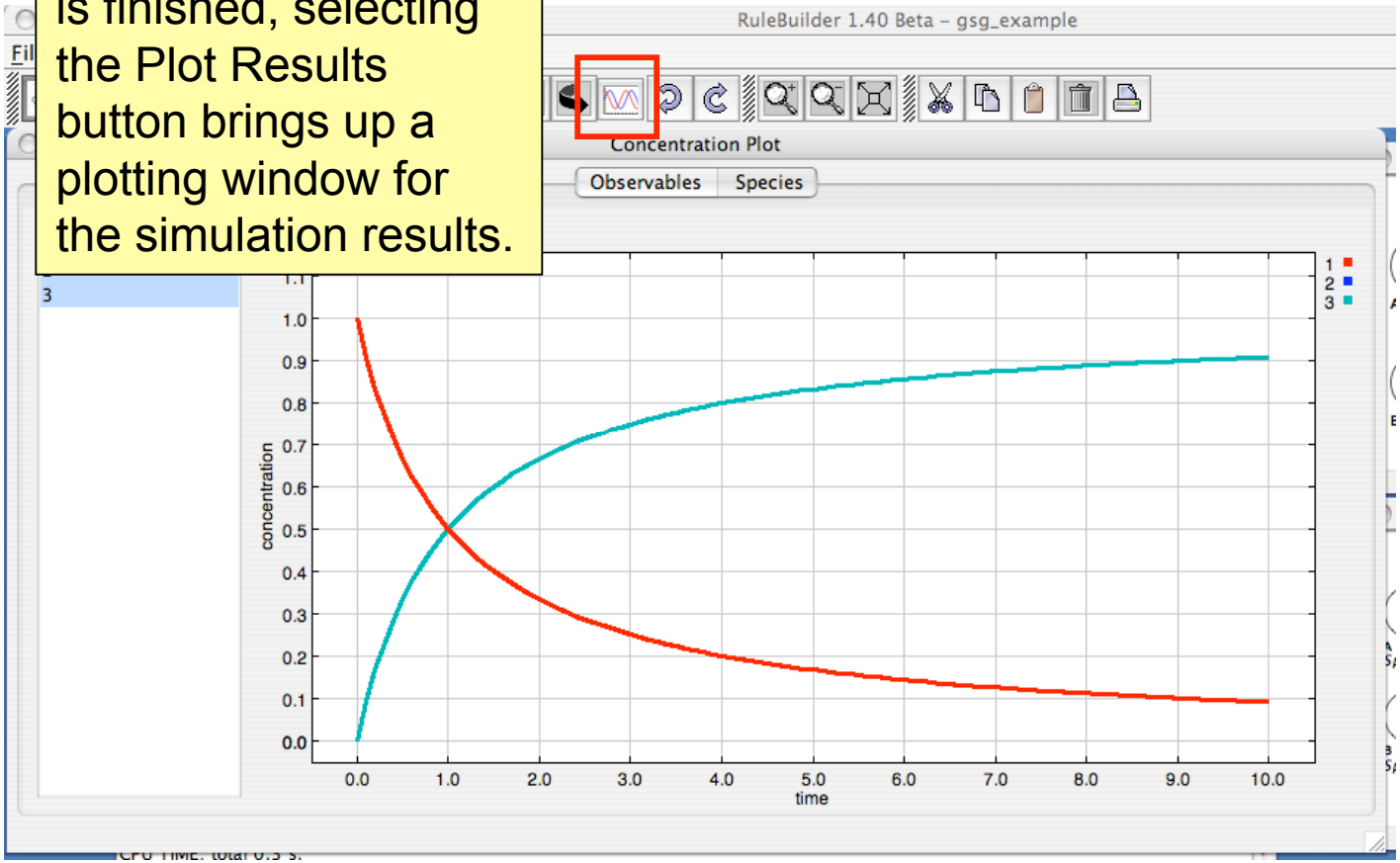
The Log Window

Running the simulation brings up the BioNetGen Output Log or Log Window

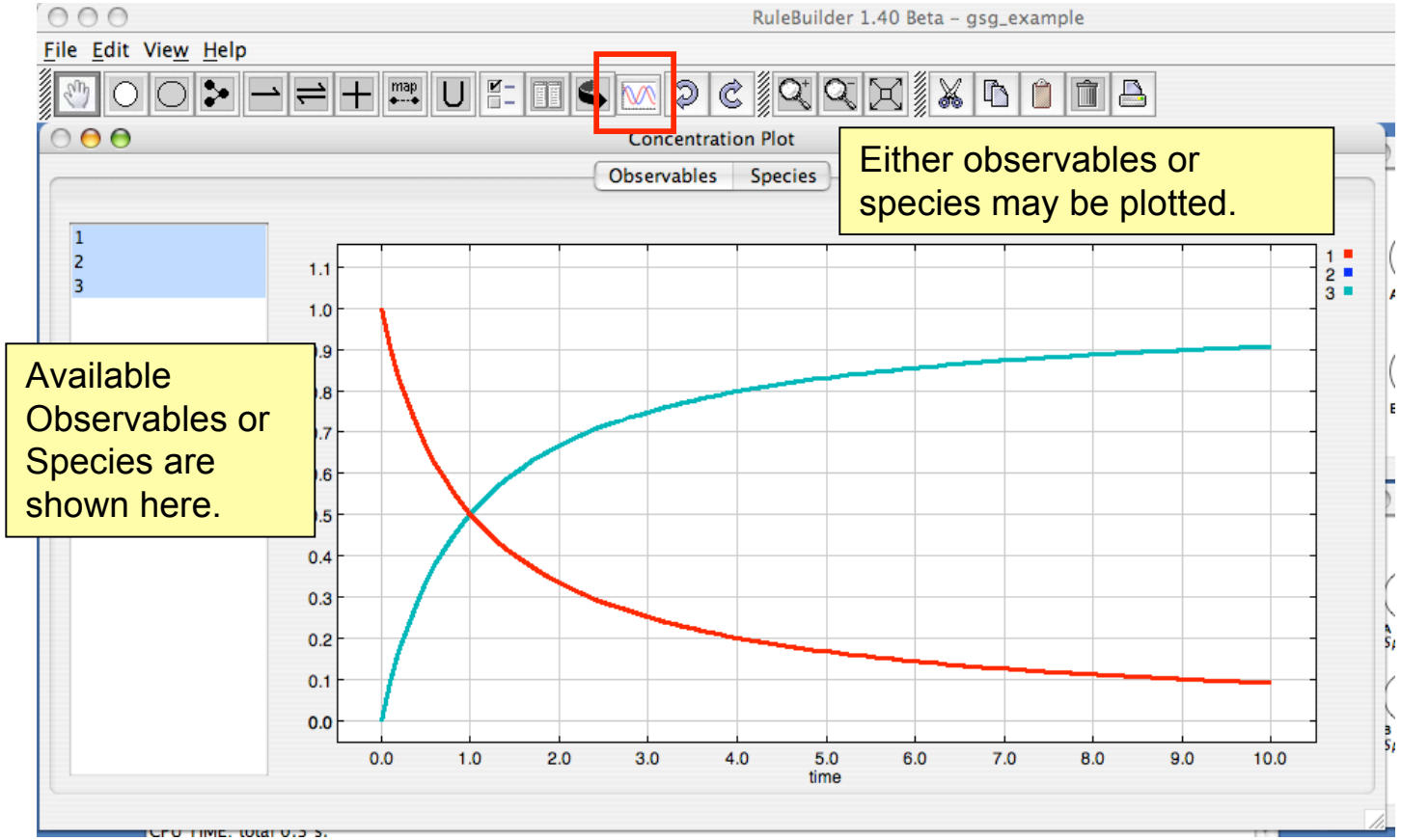


Plotting the Results

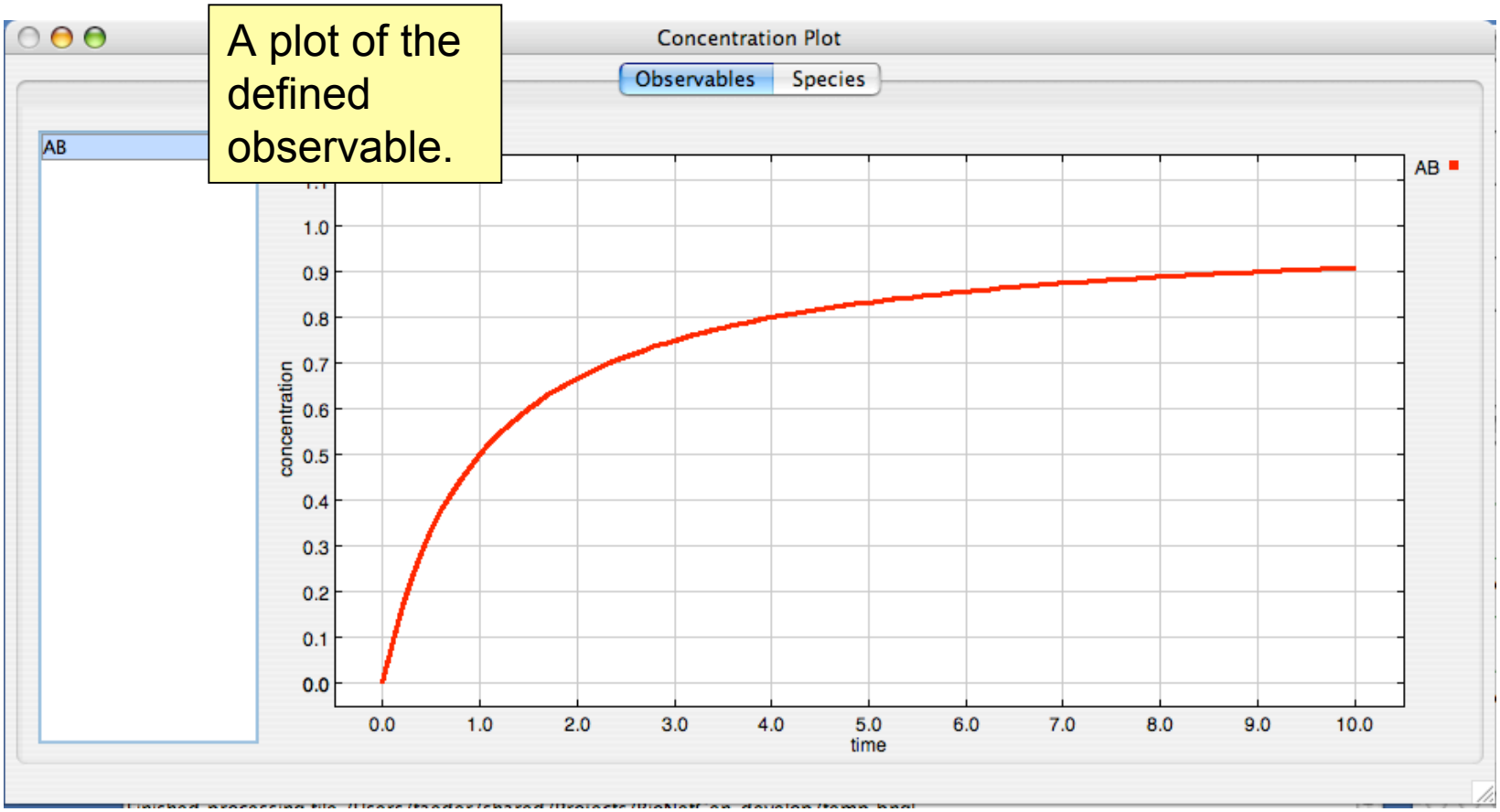
Once the simulation is finished, selecting the Plot Results button brings up a plotting window for the simulation results.

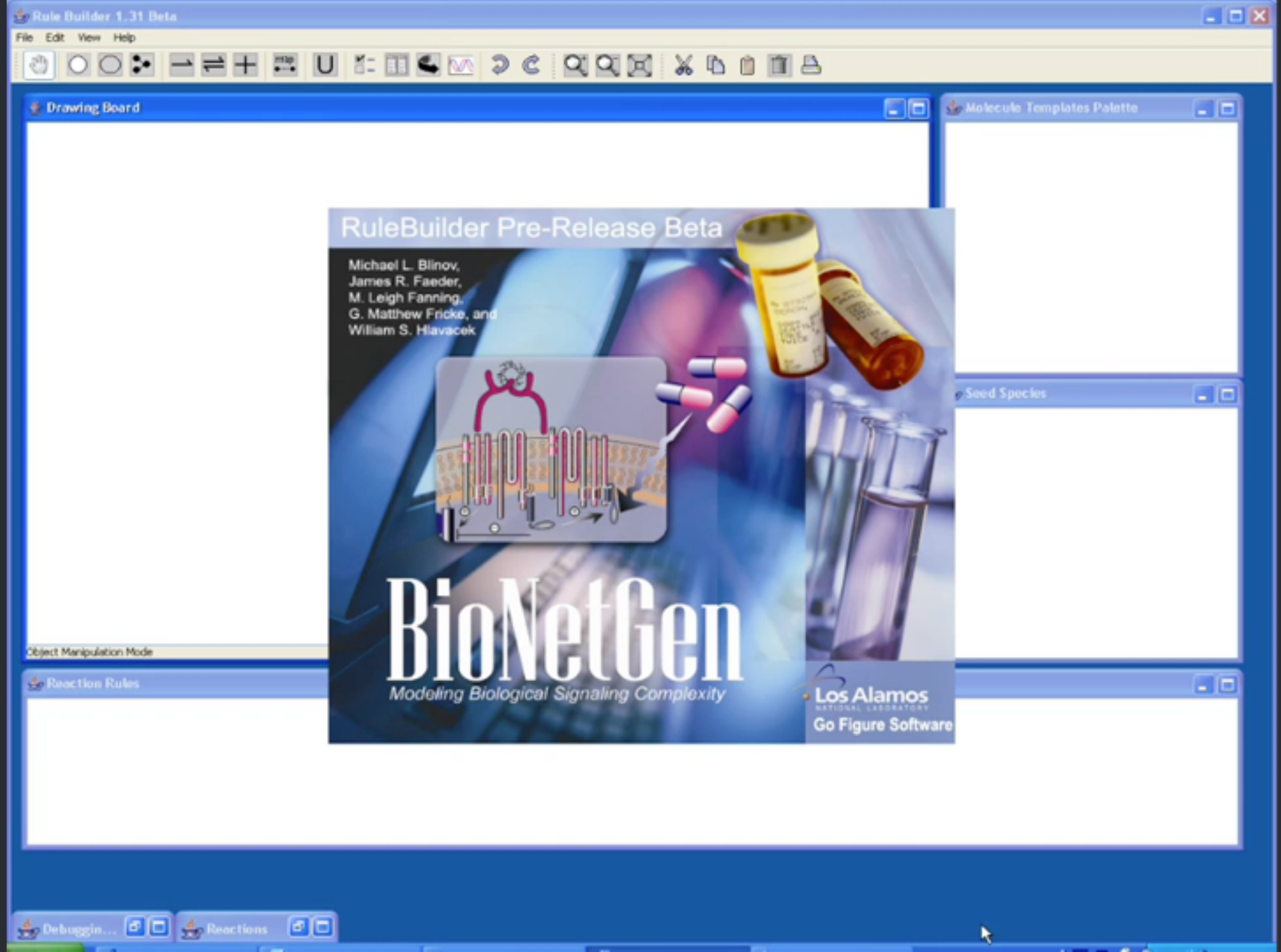


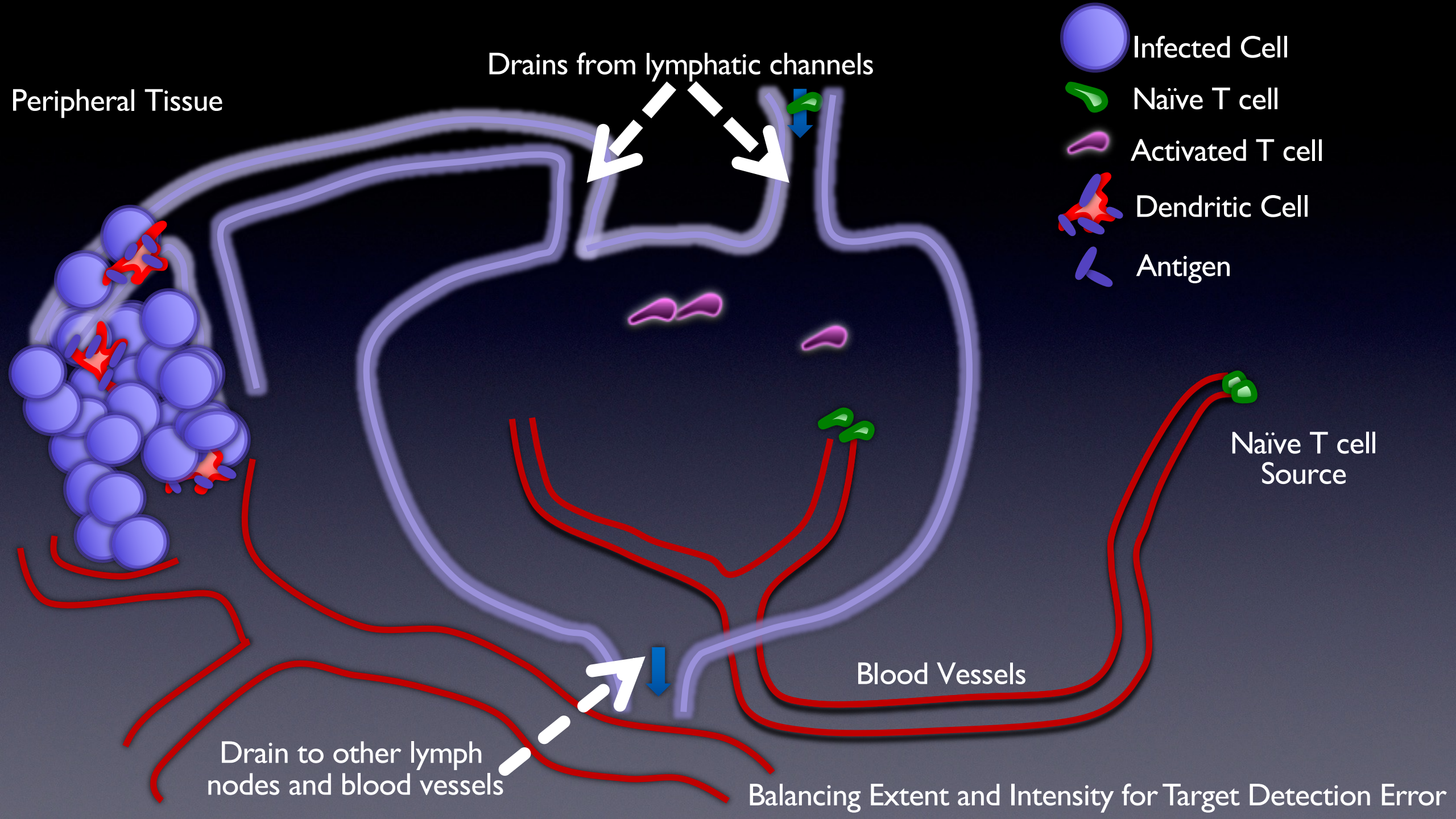
Plotting the Results



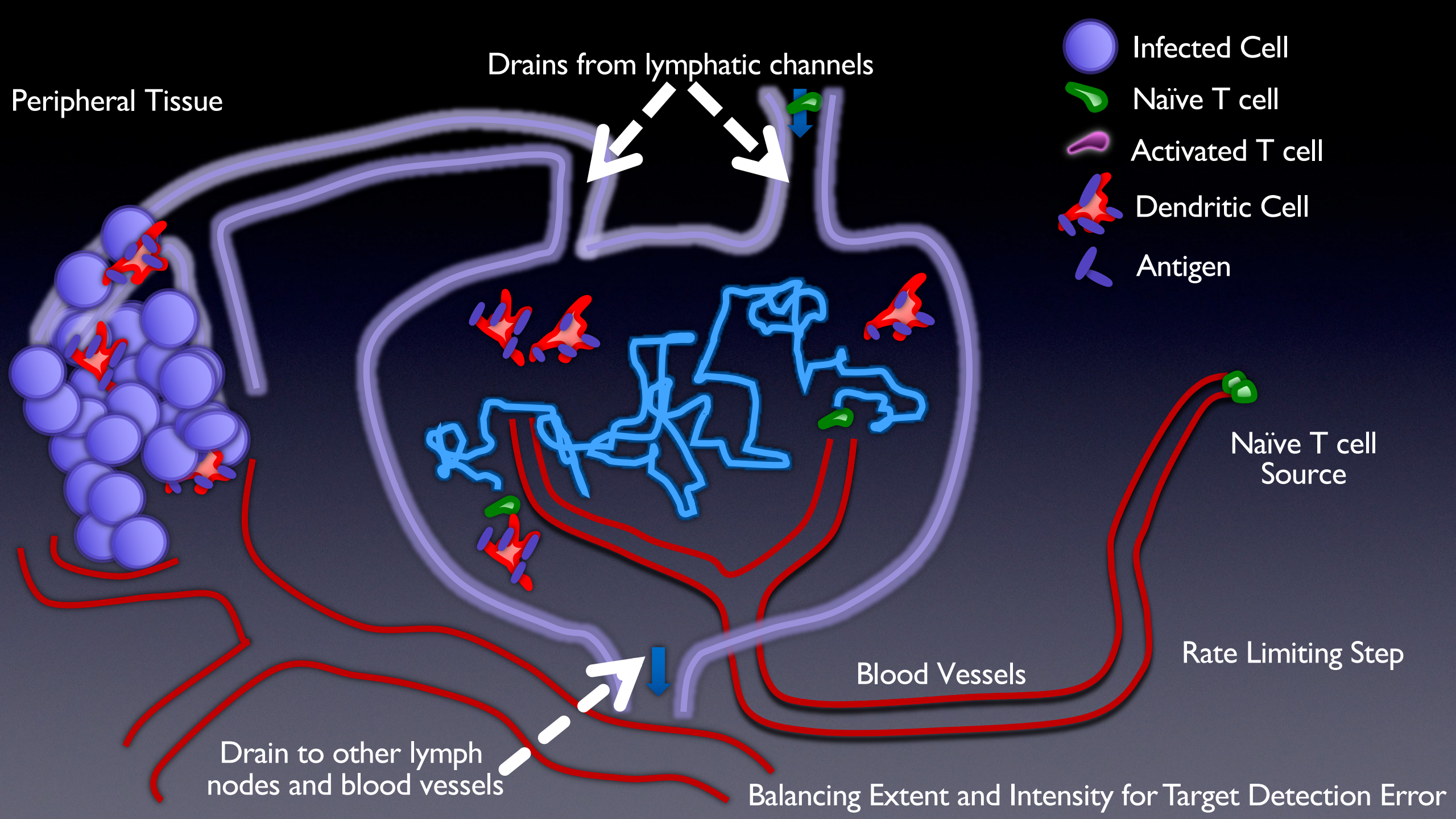
Plotting the Results

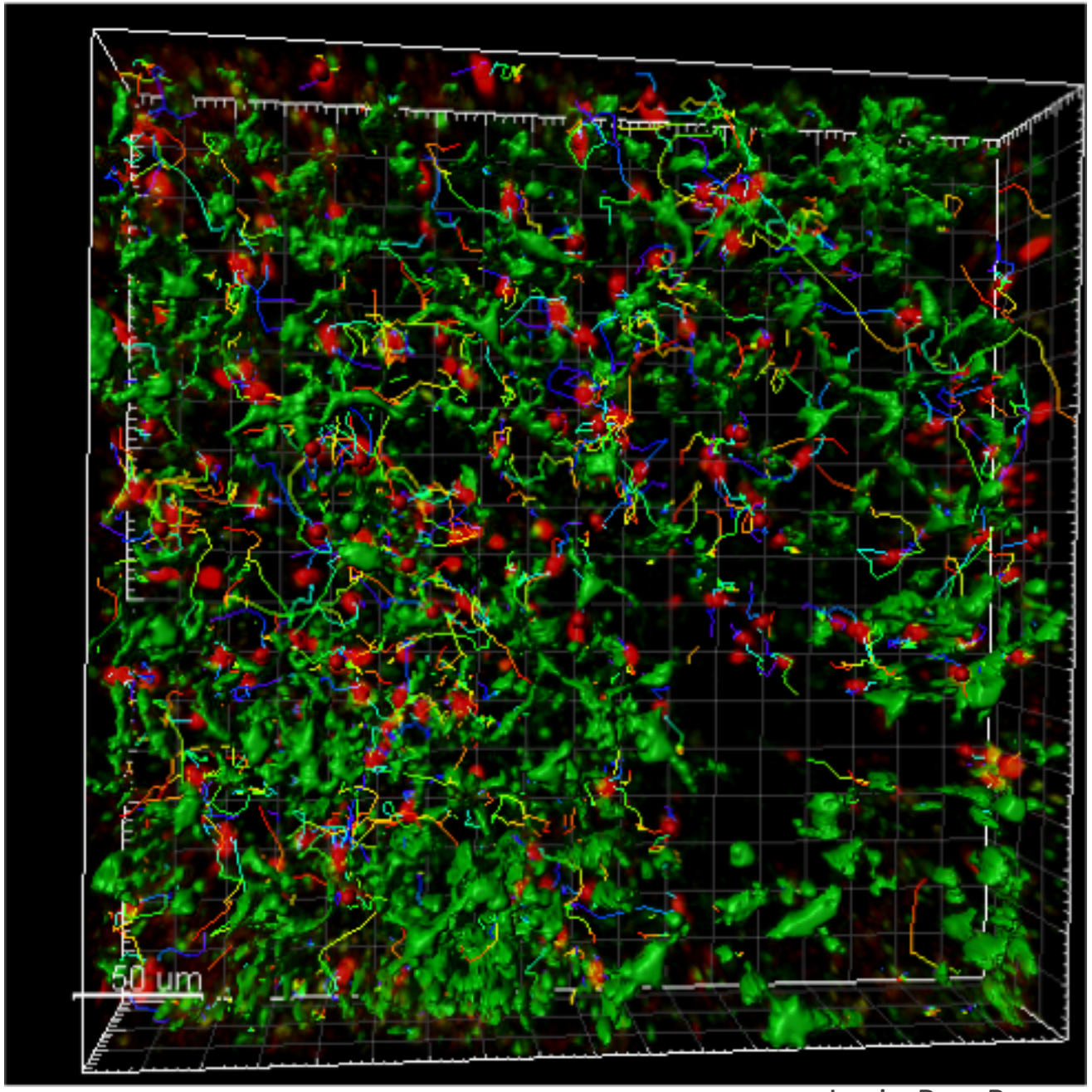



Rule Builder 1.31 Beta
File Edit View Help
Drawing Board
Molecule Templates Palette
Seed Species
Reaction Rules
Object Manipulation Mode
RuleBuilder Pre-Release Beta
Michael L. Blinov,
James R. Faeder,
M. Leigh Fanning,
G. Matthew Fricke, and
William S. Hlavacek
BioNetGen
Modeling Biological Signaling Complexity
Los Alamos
NATIONAL LABORATORY
Go Figure Software
Debuggin...
Reactions



Balancing Extent and Intensity for Target Detection Error


Peripheral Tissue
Drains from lymphatic channels
Infected Cell
Naïve T cell
Activated T cell
Dendritic Cell
Antigen
Naïve T cell Source
Blood Vessels
Rate Limiting Step
Drain to other lymph nodes and blood vessels
Balancing Extent and Intensity for Target Detection Error



Janie Rae Byrum

The Needle in a Haystack

Lymph nodes have a volume 10^6 times that of T cells.

100k T cells and 100k DCs. Small set of these are congnate.

T cells move at an average speed of of 0.11 µm/s.

T cells searching systematically (raster scan) would discover an antigen target in 6 days on average.

Simple random walkers (Brownian) have an expected 30% success rate after 3 days.[1]

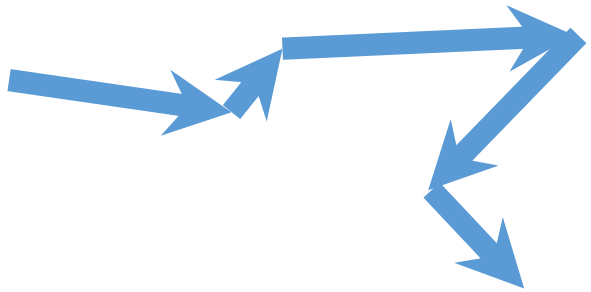
T cells are able to find cognate antigen in 3-8 hours and give up after 12-24 hours.

<-- DCs in green, T cells in red

[1] Preston, S. P., et al. "T-cell motility in the early stages of the immune response modeled as a random walk amongst targets." *Physical Review E* 74.1 (2006): 011910.

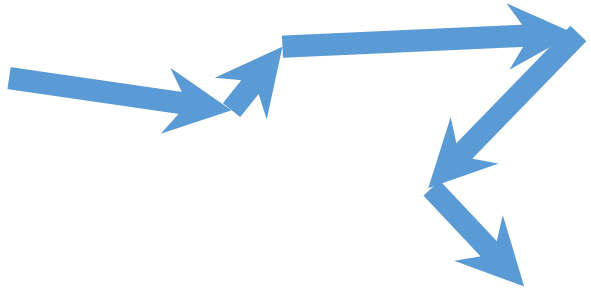
Background: Intensive vs Extensive Search

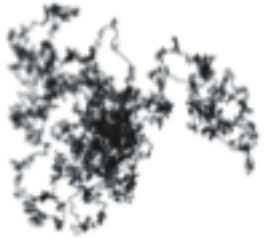
- We can describe any stochastic search pattern with distributions of vector lengths and turning angles.



Background: Intensive vs Extensive Search

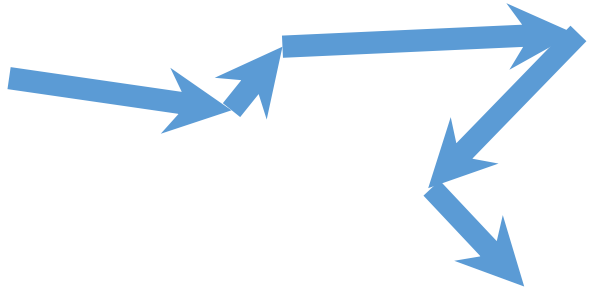
- We can describe any stochastic search pattern with distributions of vector lengths and turning angles.
- Intensive searchers have lower displacement but search more thoroughly.
- Simple random search (Brownian motion) will eventually cover the entire area.

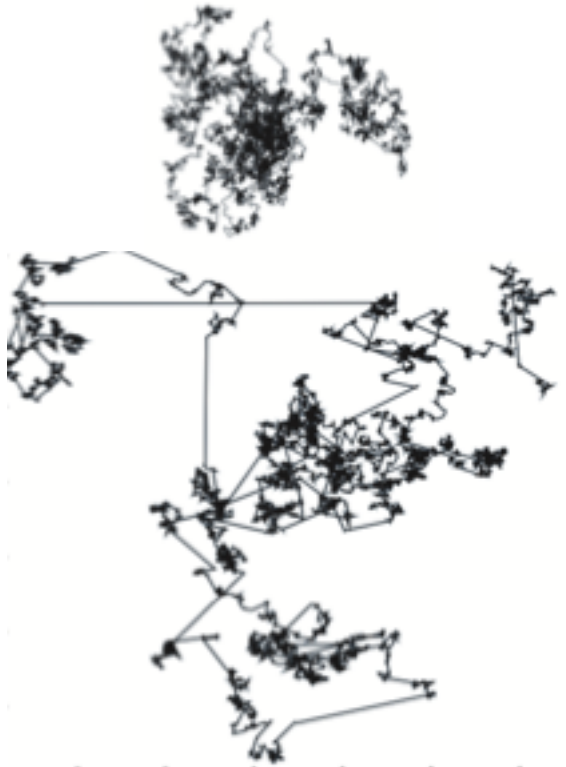




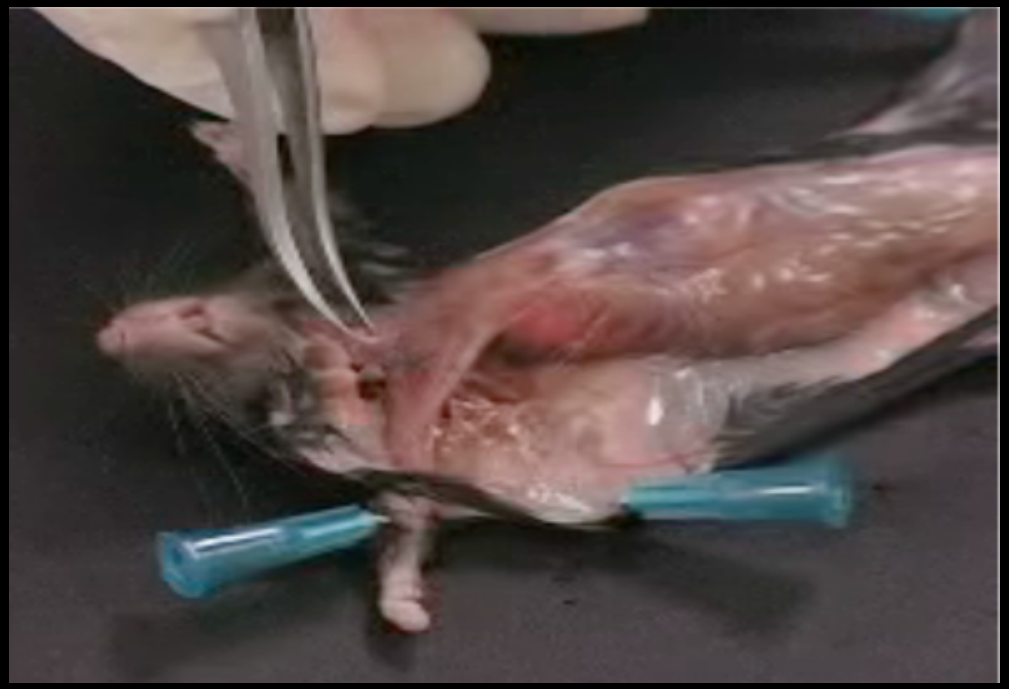
Background: Intensive vs Extensive Search

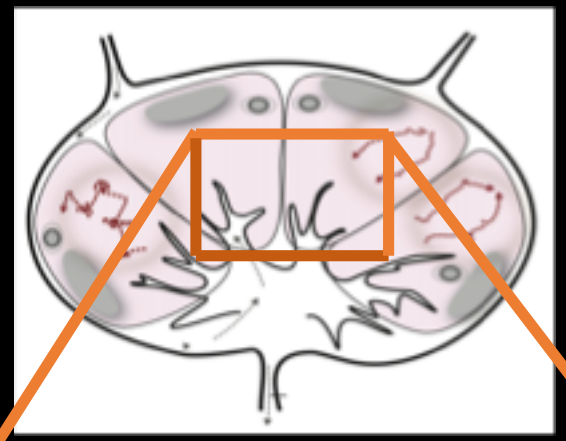
- We can describe any stochastic search pattern with distributions of vector lengths and turning angles.
- *Intensive* searchers have lower displacement but search more thoroughly.
- Simple random search (Brownian motion) will eventually cover the entire area.

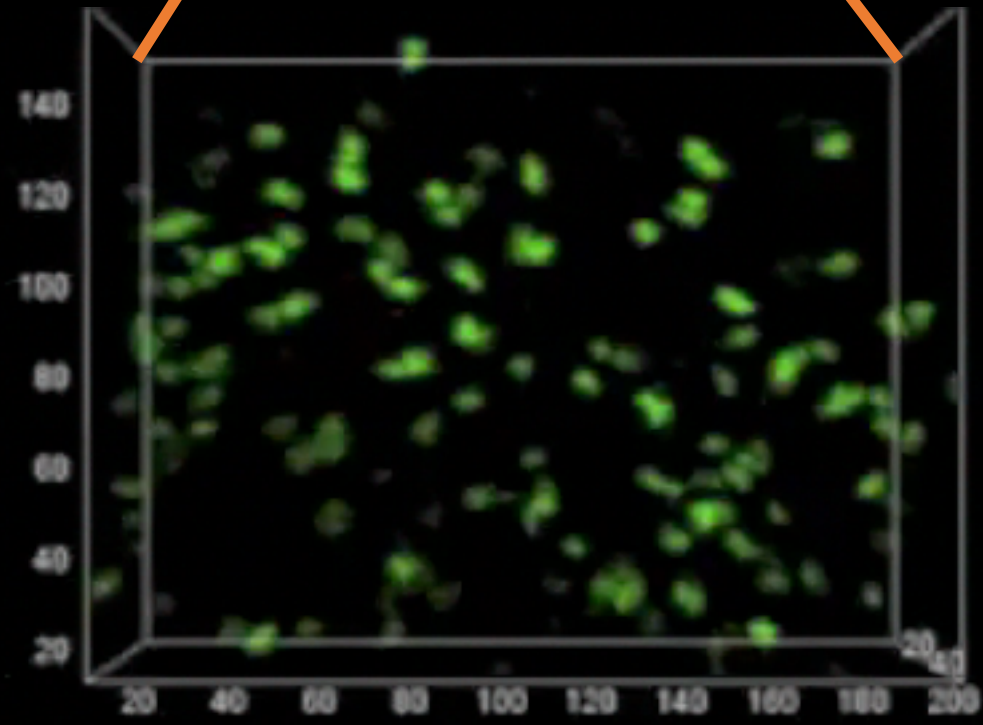




- *Extensive* searchers cover more ground but leave gaps.
- Mean Squared Displacement (MSD) is a measure of search extent

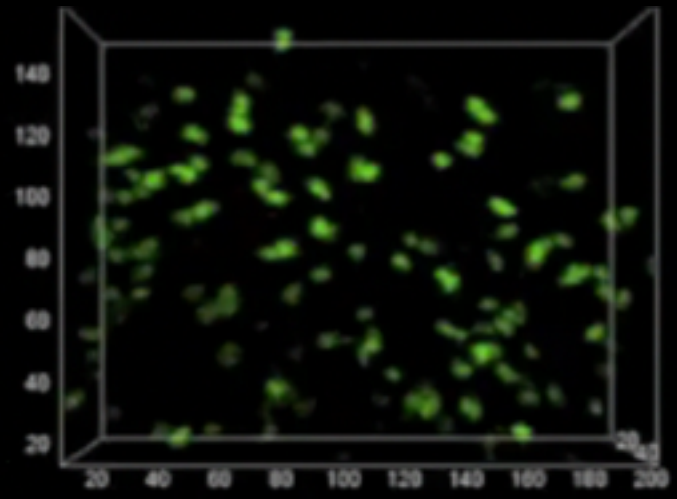


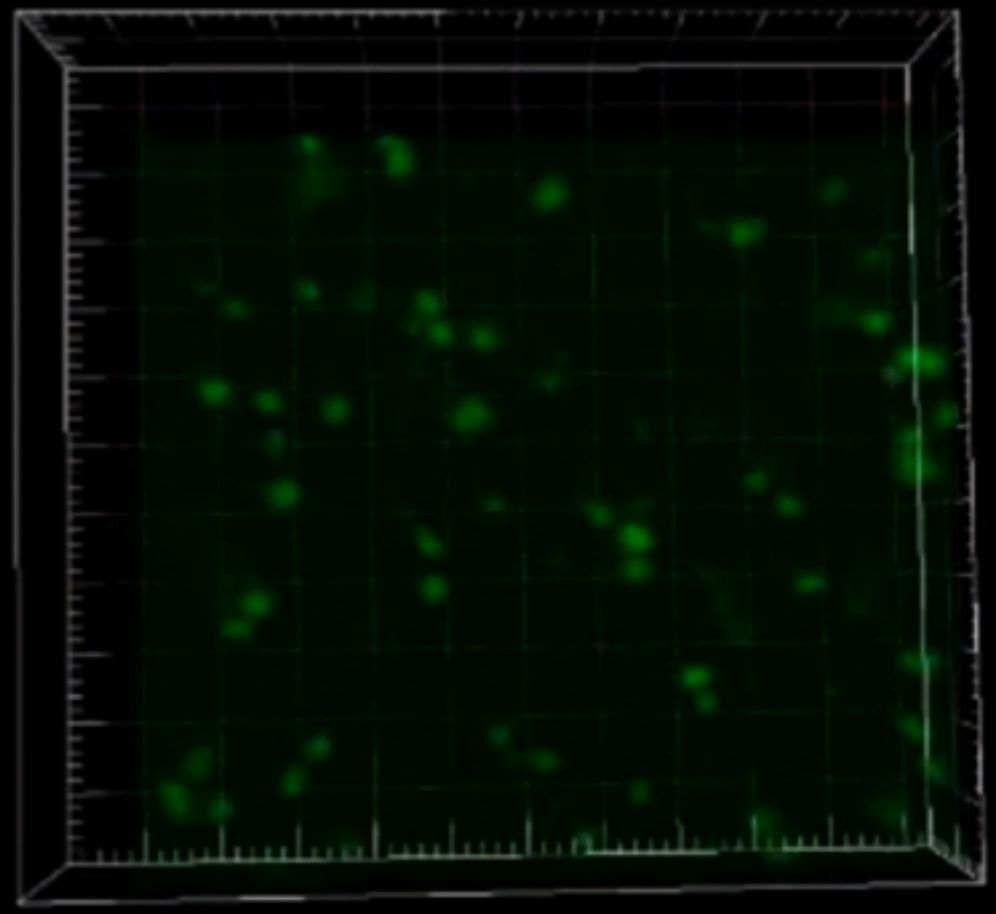


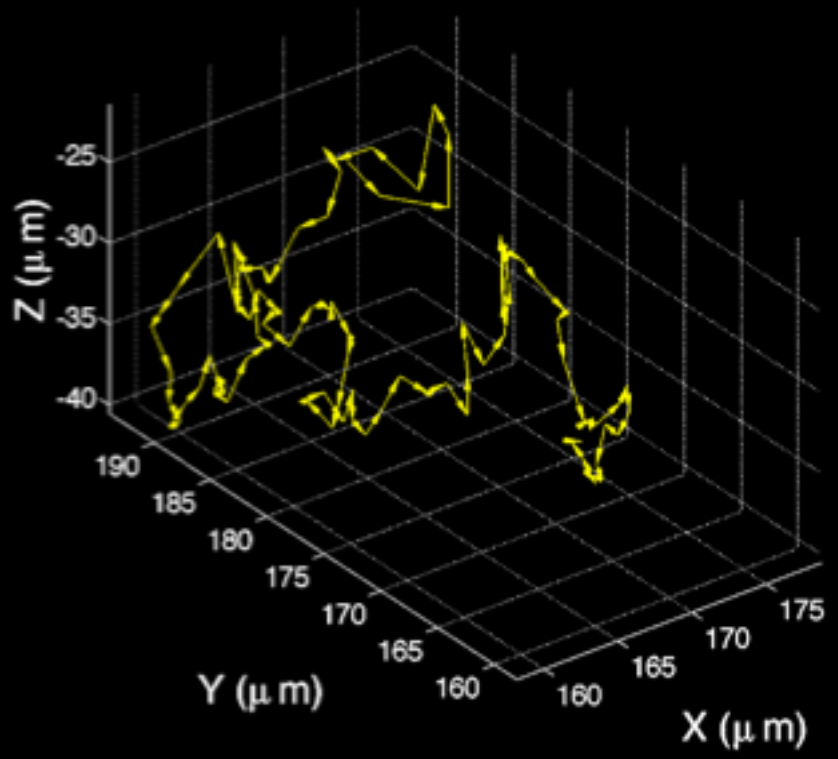


Two-photon microscopy

131 ex vivo observations
25,000 T cells tracked
Half hour observations

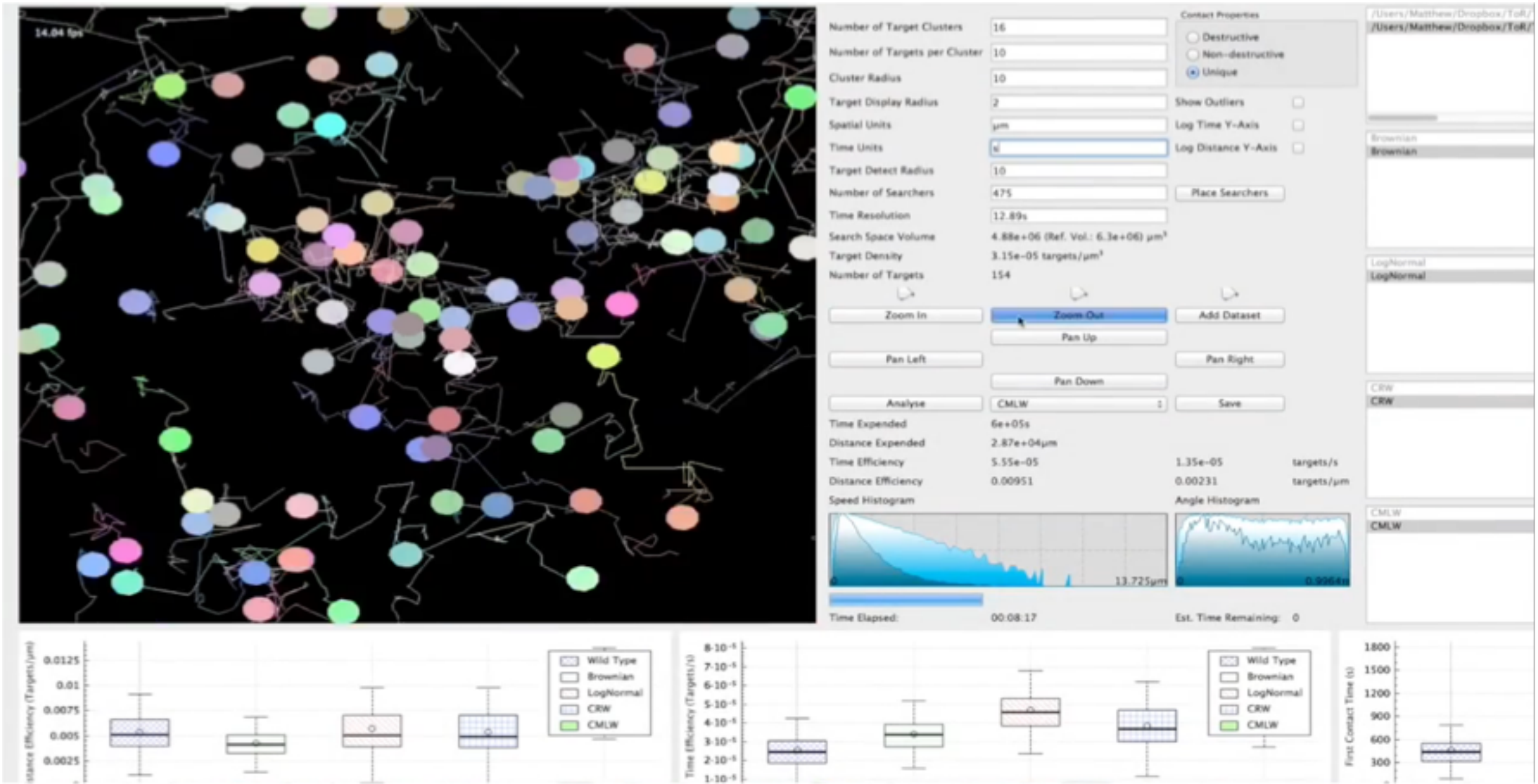






Extracting Tracks from Fluorescence
in collaboration with the Cannon lab

Building a statistical model of T cell Search



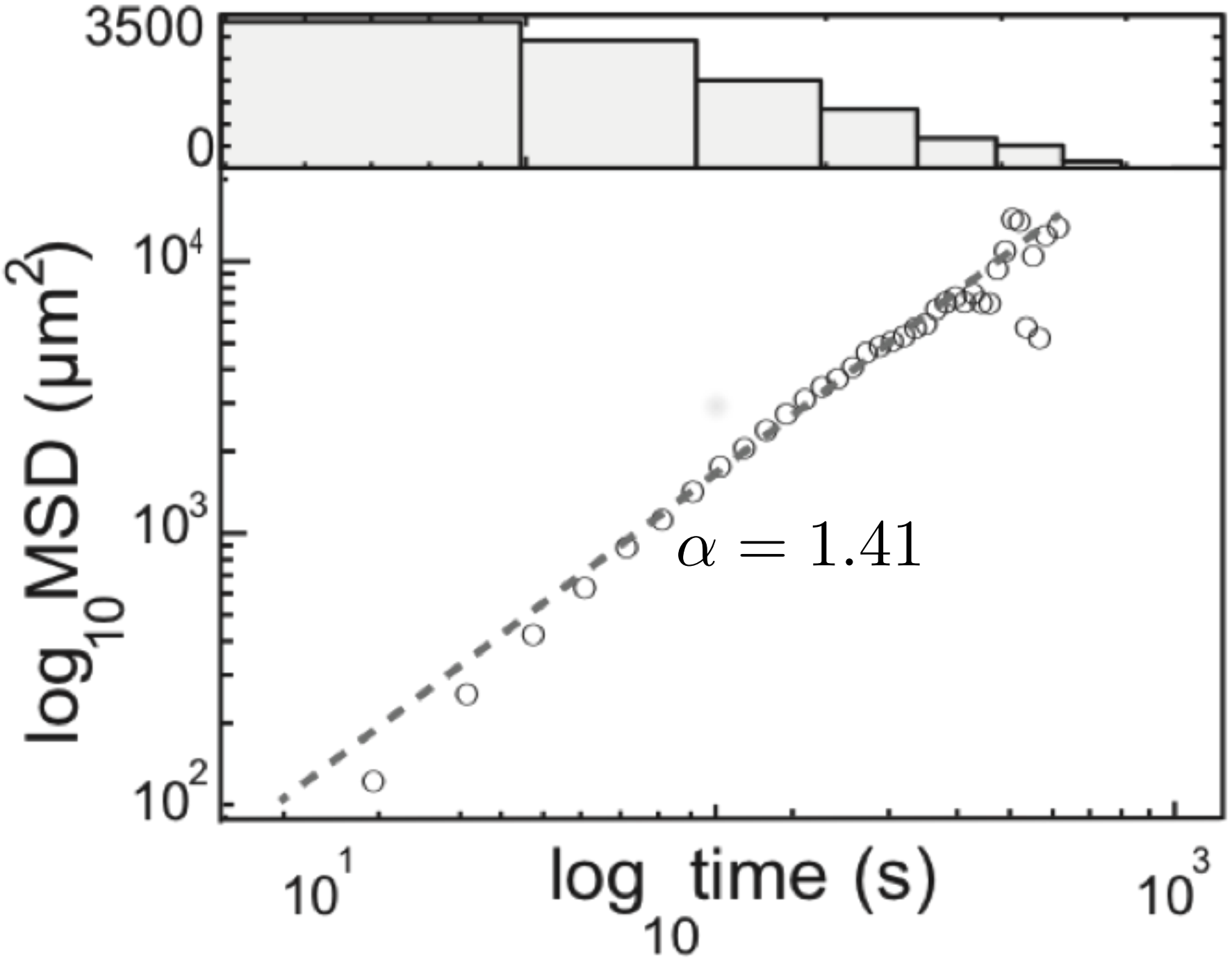
Displacement: Distance travelled from starting position.

Simple random walk
Would have a log transformed MSD with slope α =1 and $\mathcal{H}$ = 2.

We see a slope of α =1.41
Superdiffusion.

Fractal dimension = 1.41

(This is our measure of the *intensity-extent trade-off*)

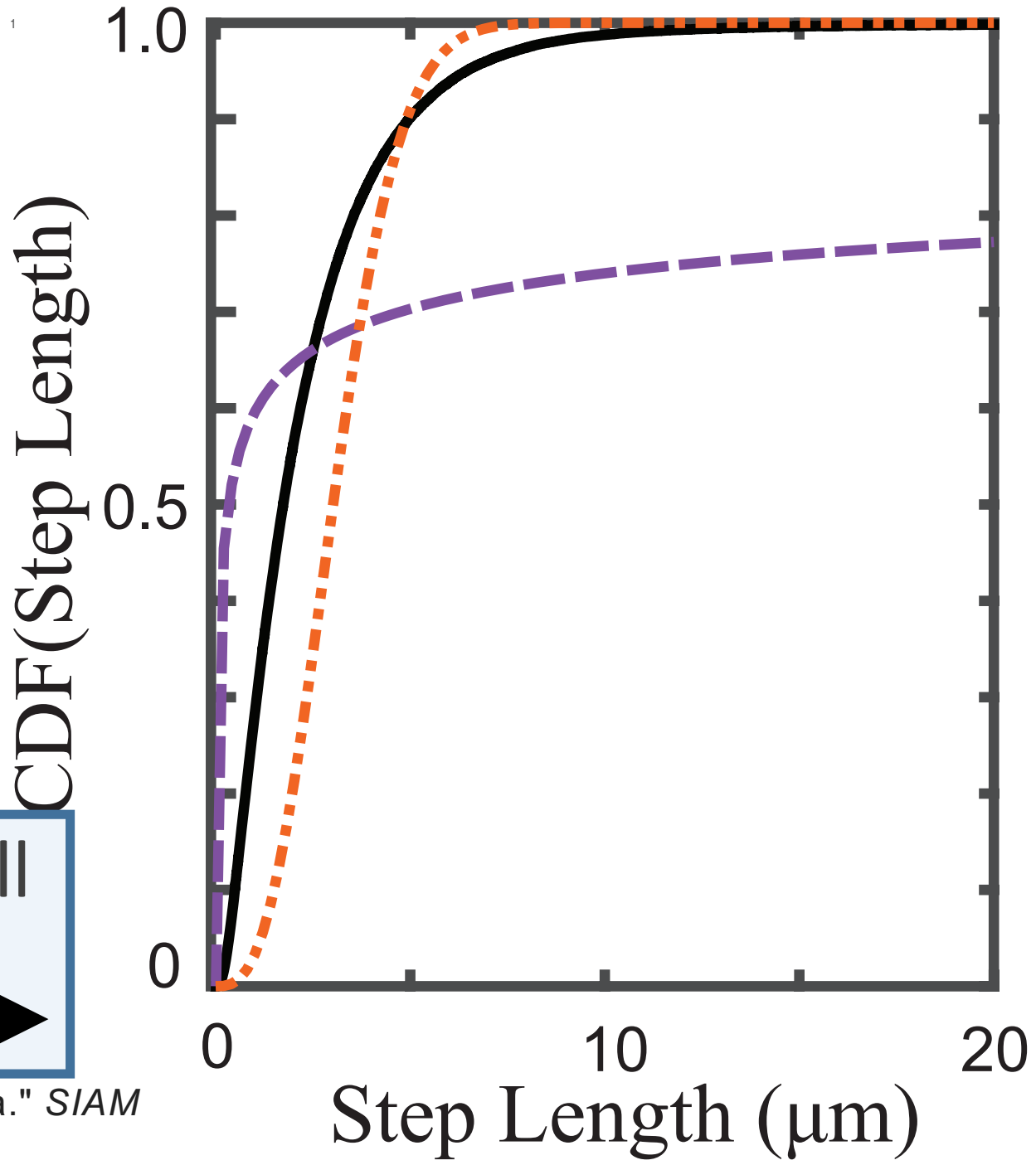


Modelling T cell Search: Fit Step Lengths

Observed

Power Law

Maxwell



Maximum-likelihood fitting [1]

Power Law ← Extensive

Maxwell → Intensive

[1] Clauset, Aaron "Power-law distributions in empirical data." *SIAM review* (2009)

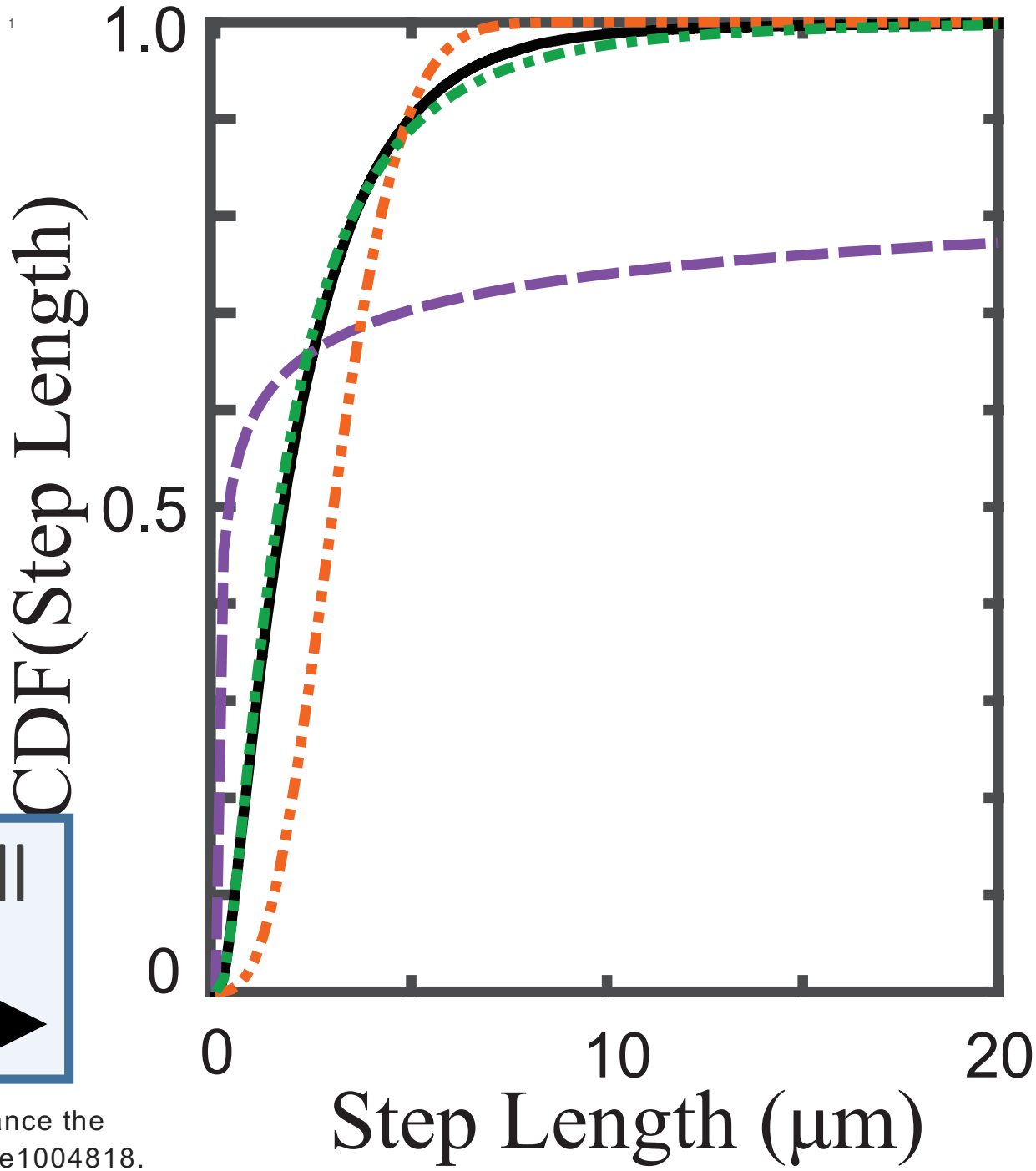
Modelling T cell Search: Fit Step Lengths

Observed

Power Law

Maxwell

Lognormal



Power Law Lognormal Maxwell

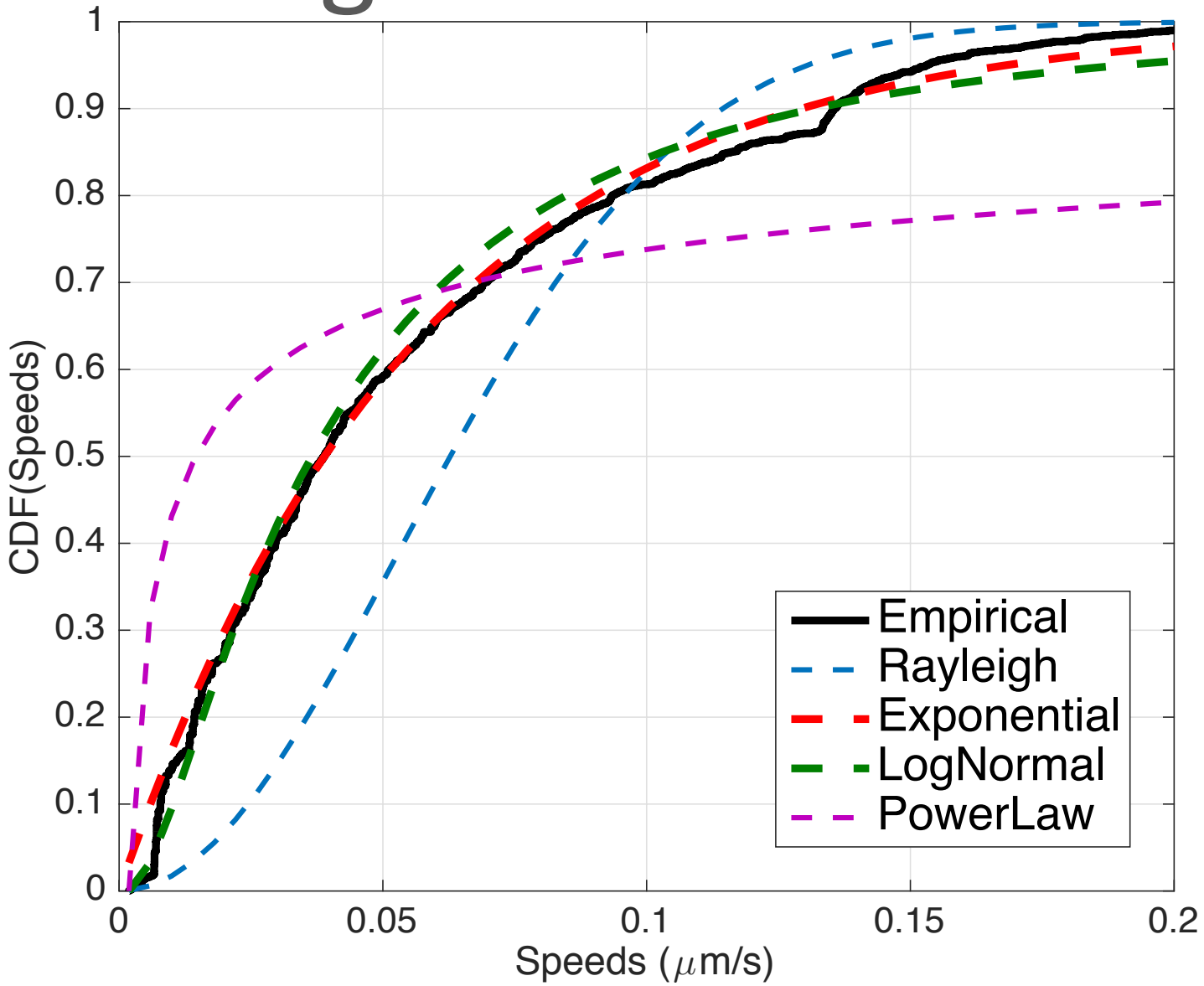
Extensive

Intensive

Fricke, G. Matthew, et al. "Persistence and adaptation in immunity: T cells balance the extent and thoroughness of search." *PLoS computational biology* 12.3 (2016): e1004818.

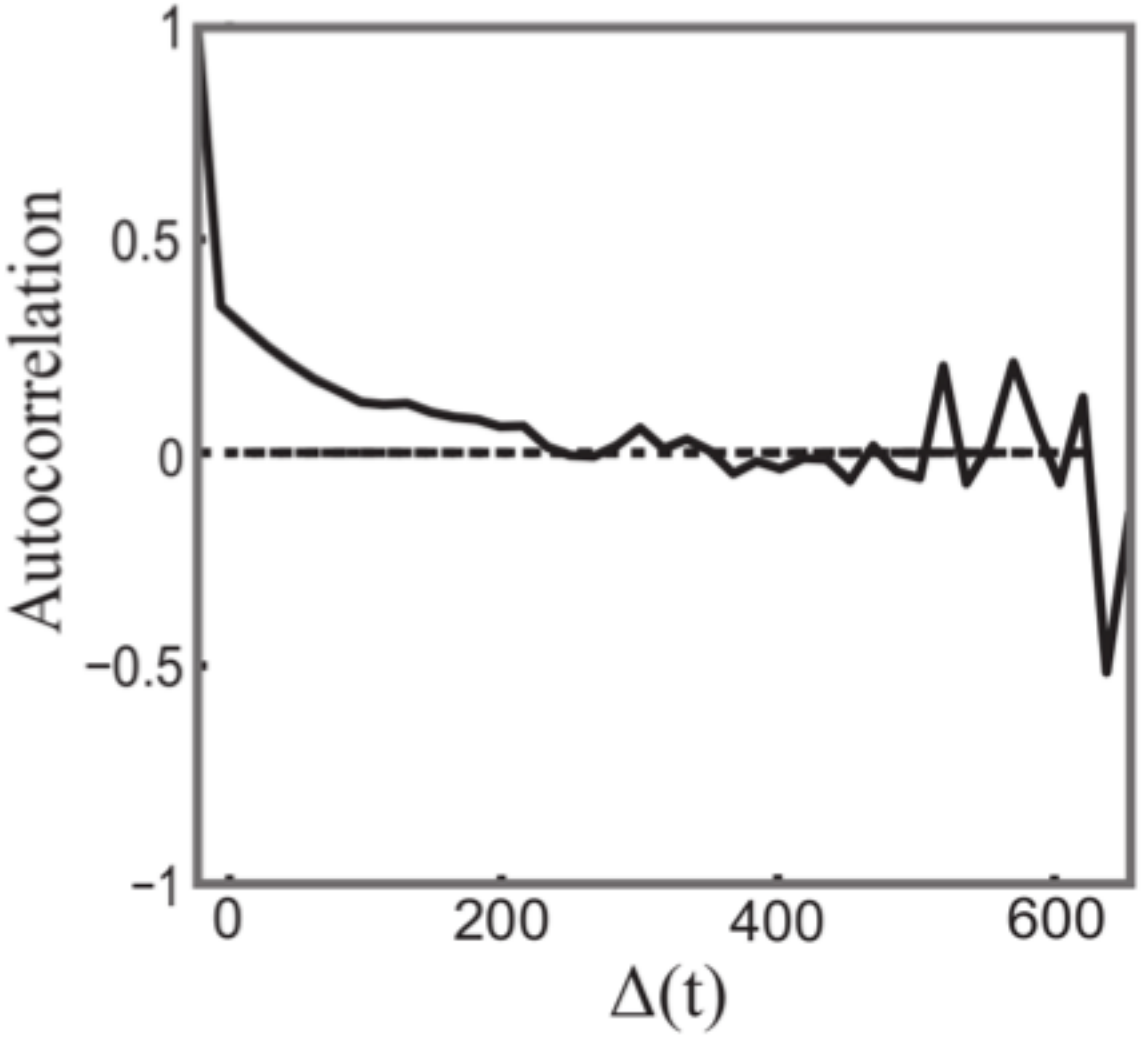
T cell Search in the Lung

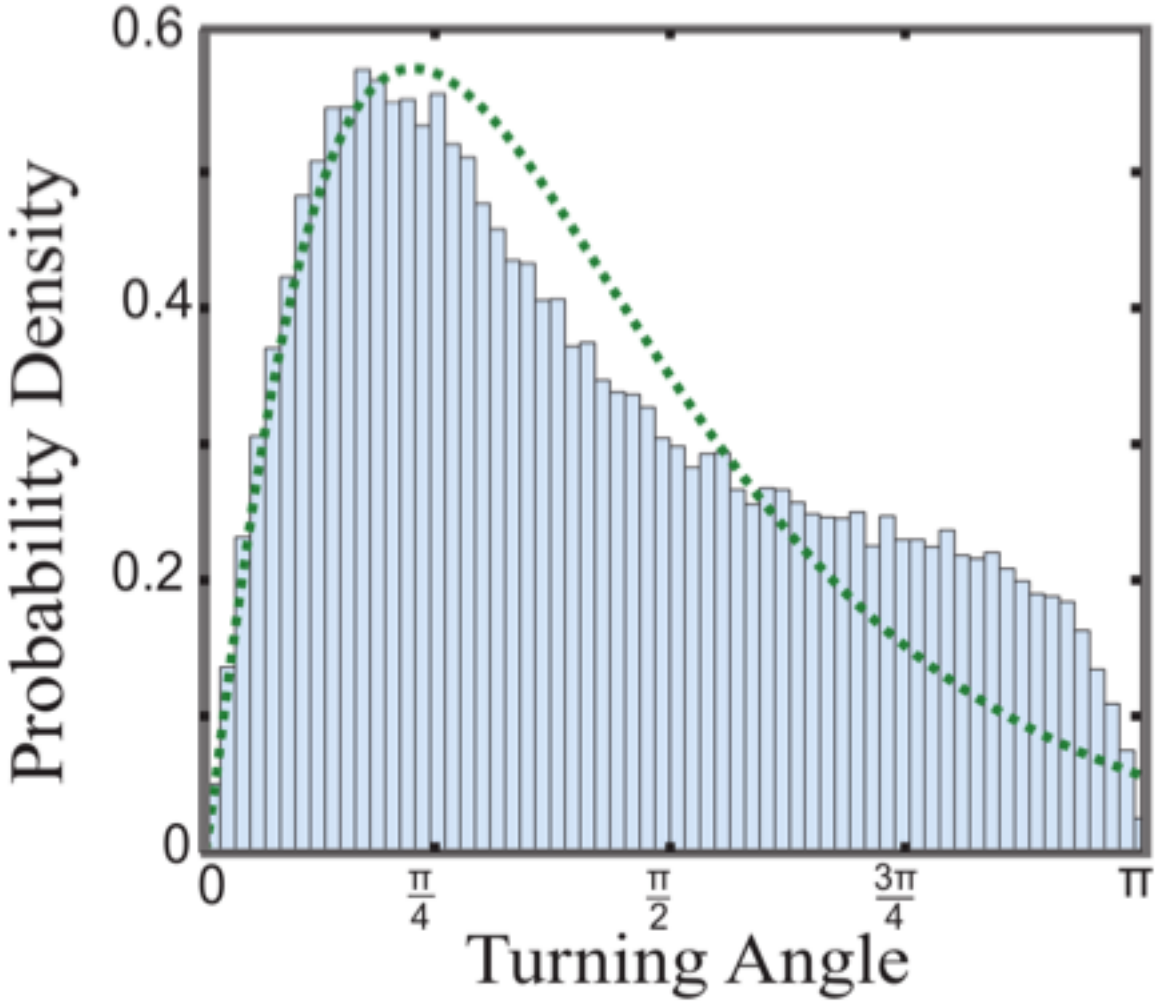
- The lognormal CDF is still a good fit.
- Exponential is also good.
- This pattern of movement is somewhat less intensive than in lymph nodes.



Paulus Mrass et al., "*ROCK regulates the intermittent mode of interstitial T cell migration in inflamed lungs,*" **Nature Communications,** 2017

Modelling T cell Search: Angle Correlation (Search in Lungs and T cells look similar)

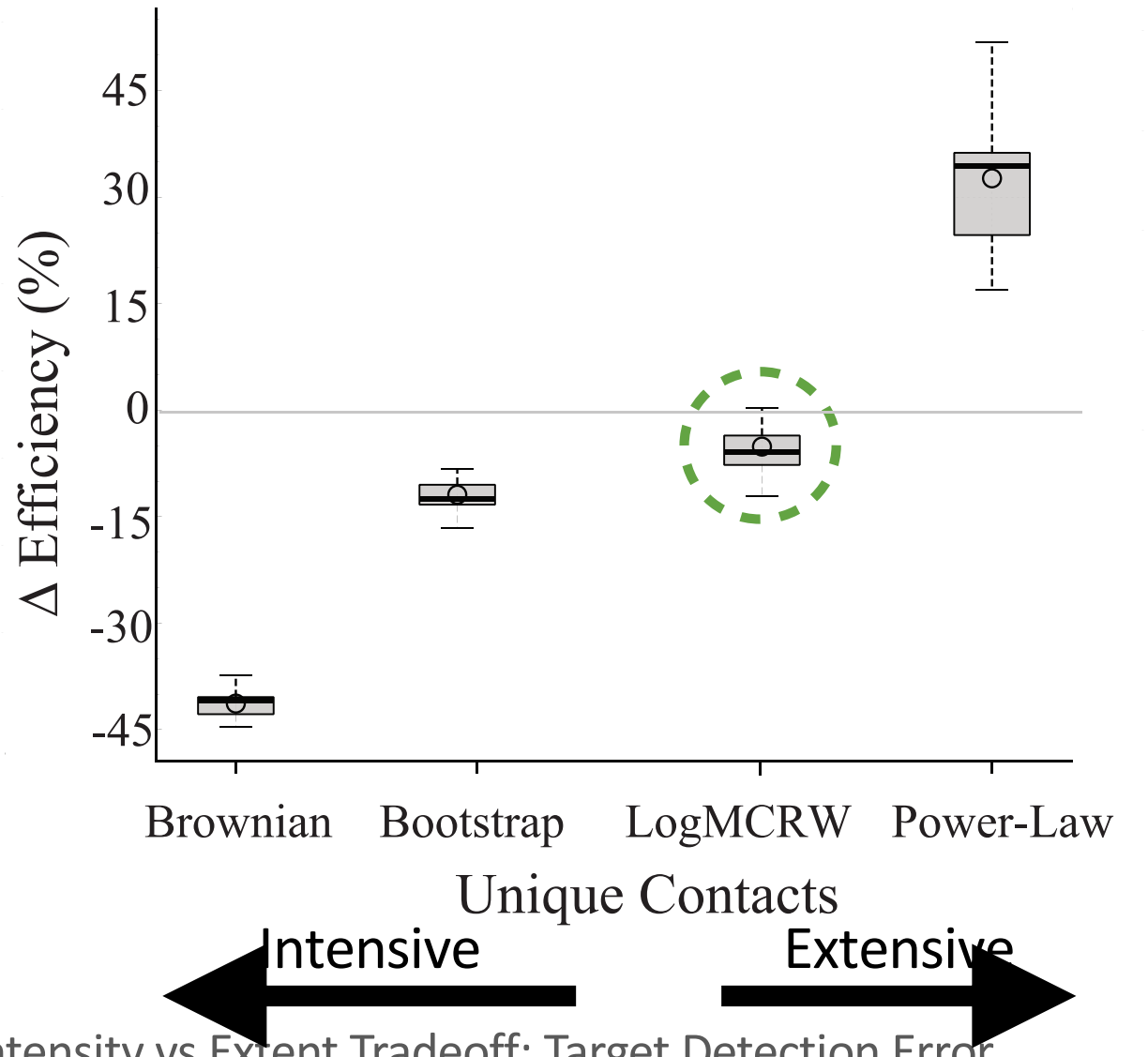




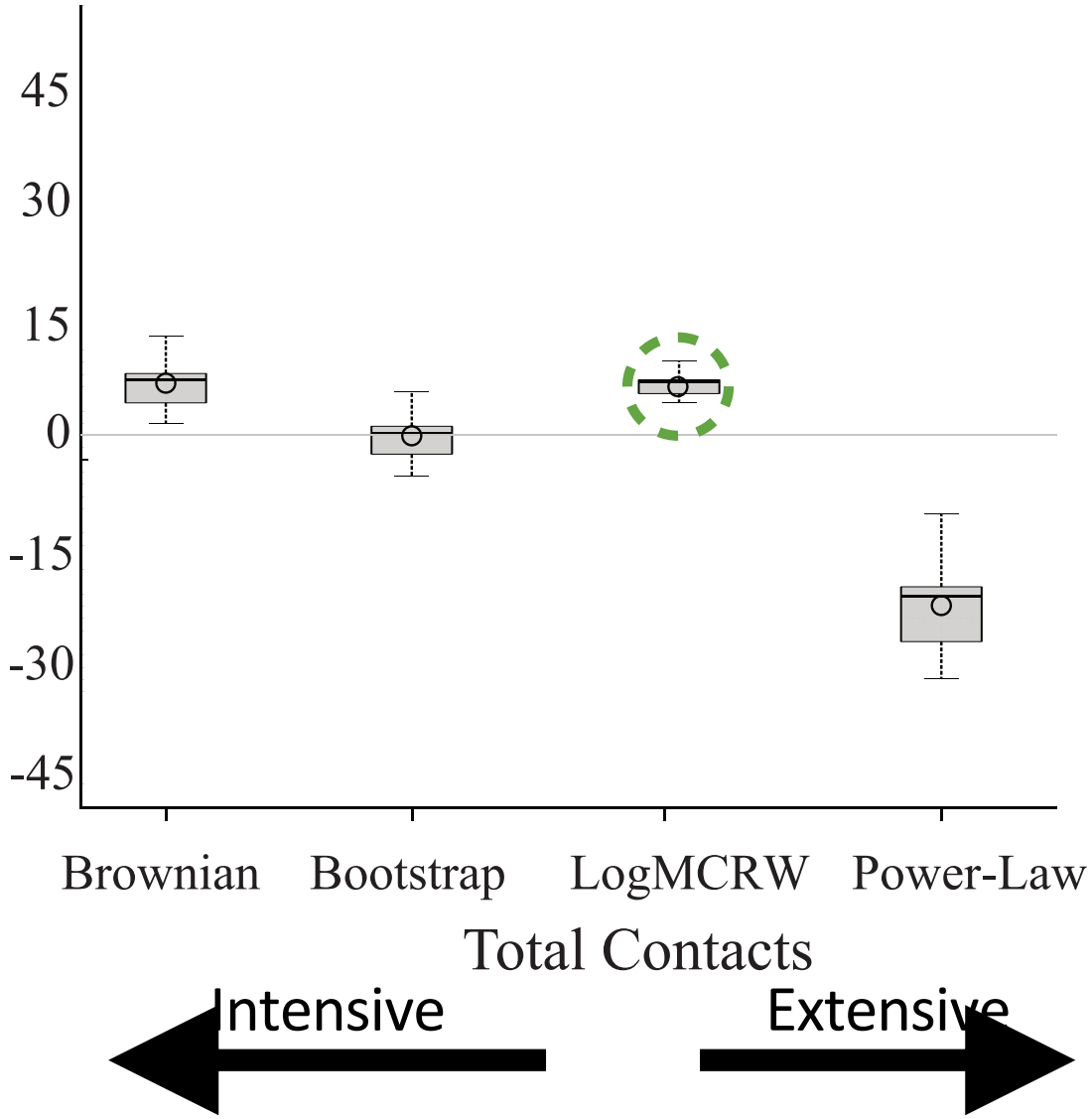
Measure of correlation with previous direction. Correlated random walk?

Comparison of search efficiency with empirical observations

Extensive search is better



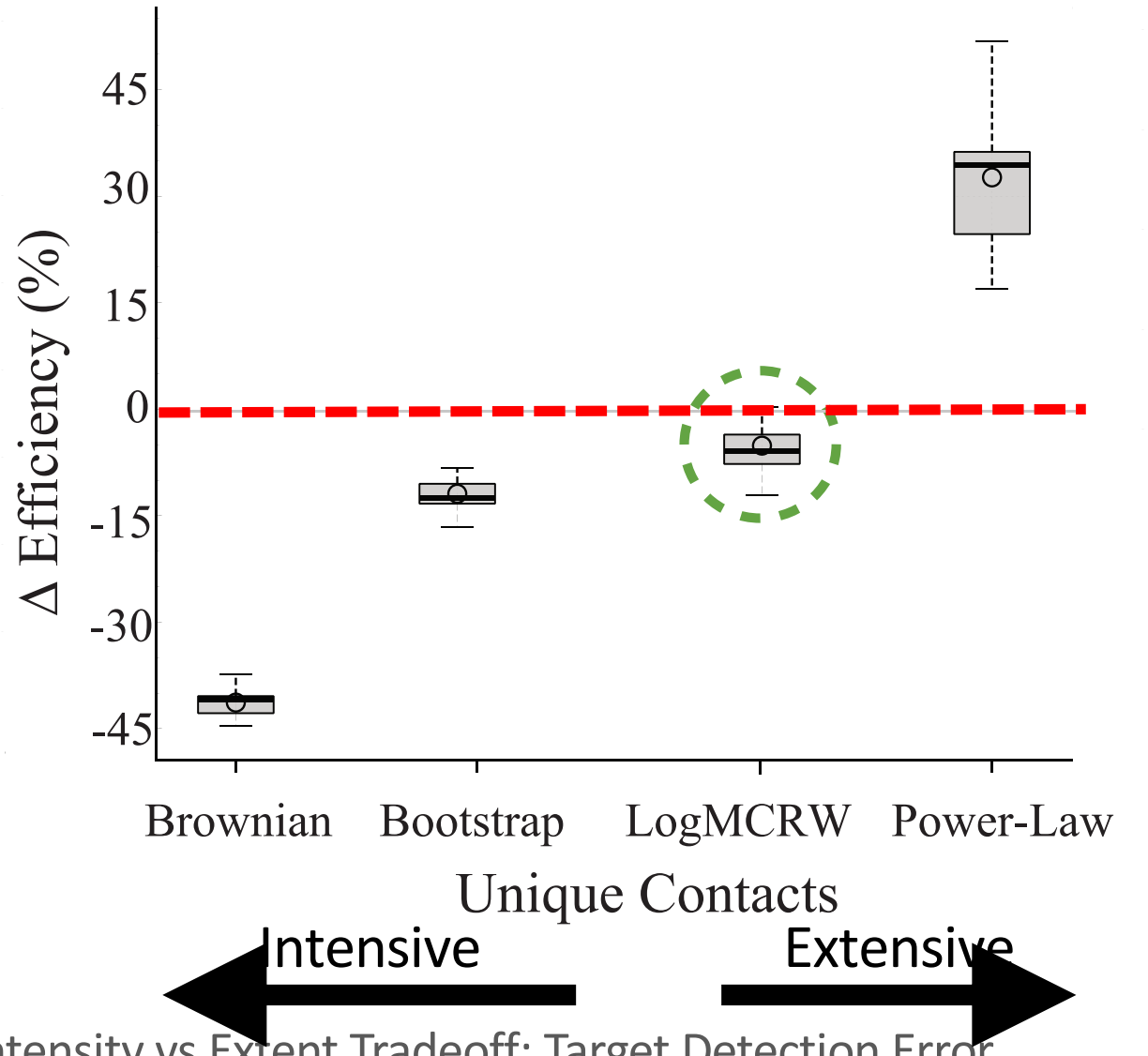
Intense search is better



Intensity vs Extent Tradeoff: Target Detection Error

Comparison of search efficiency with empirical observations

Extensive search is better



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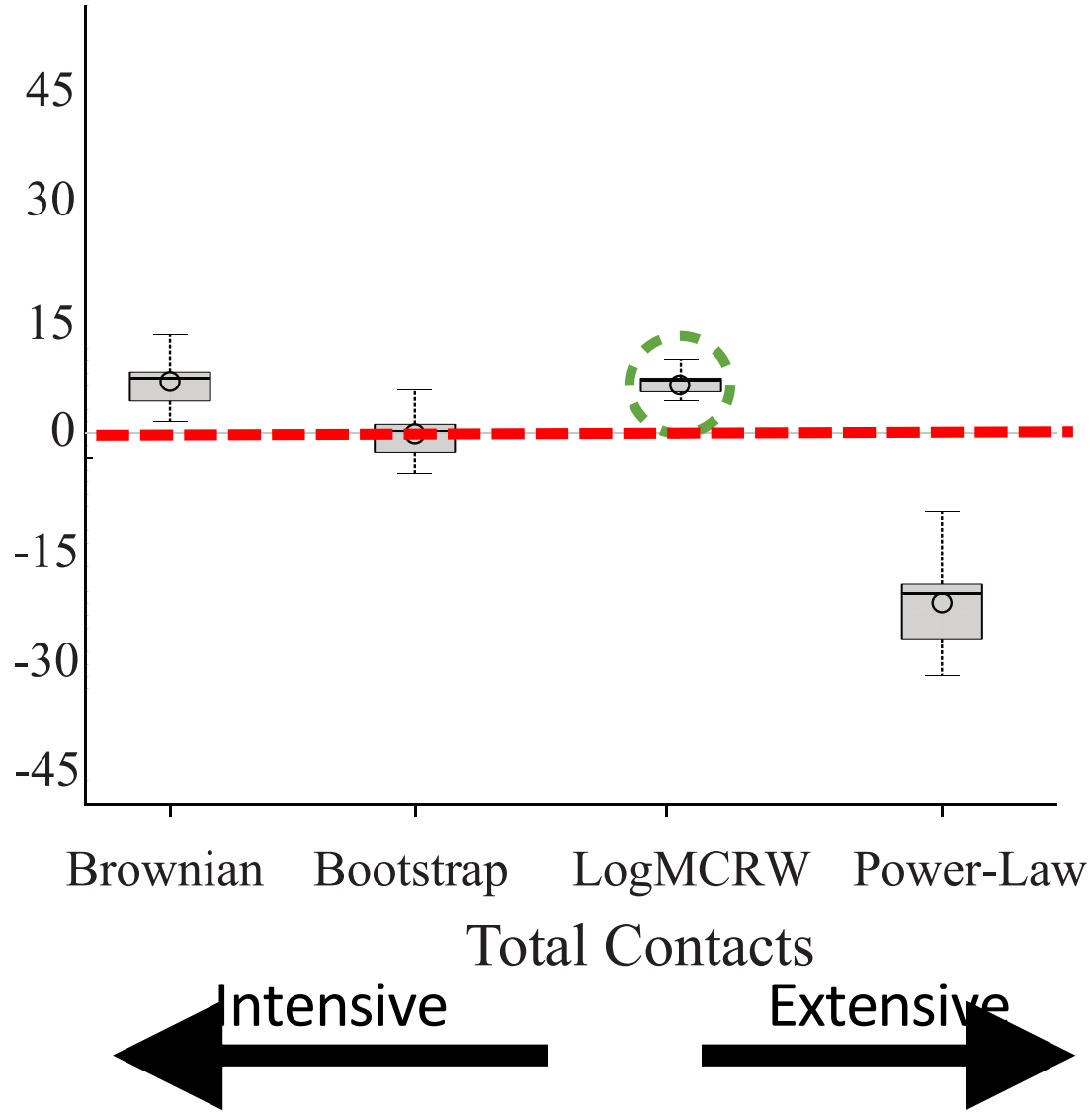

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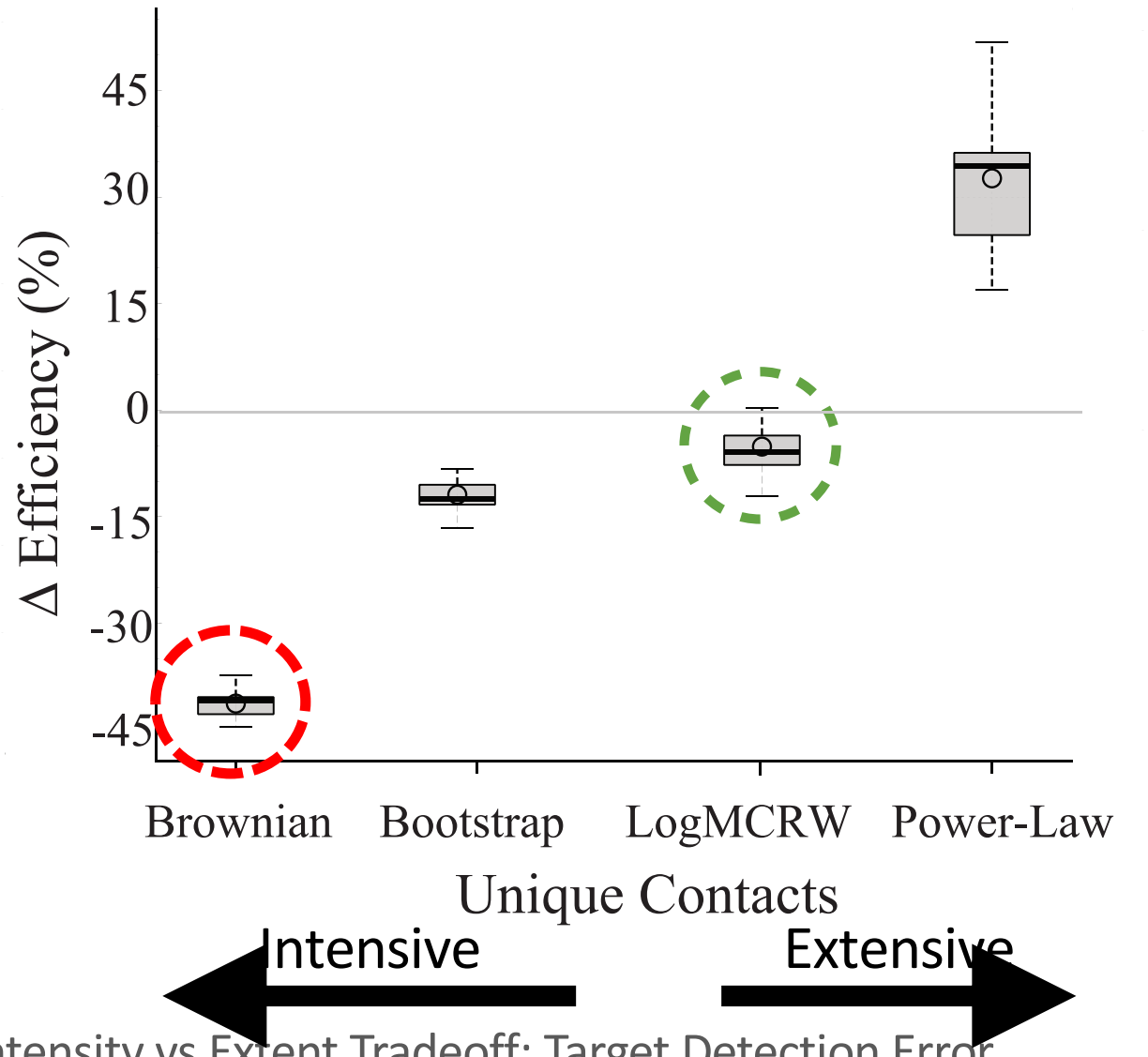

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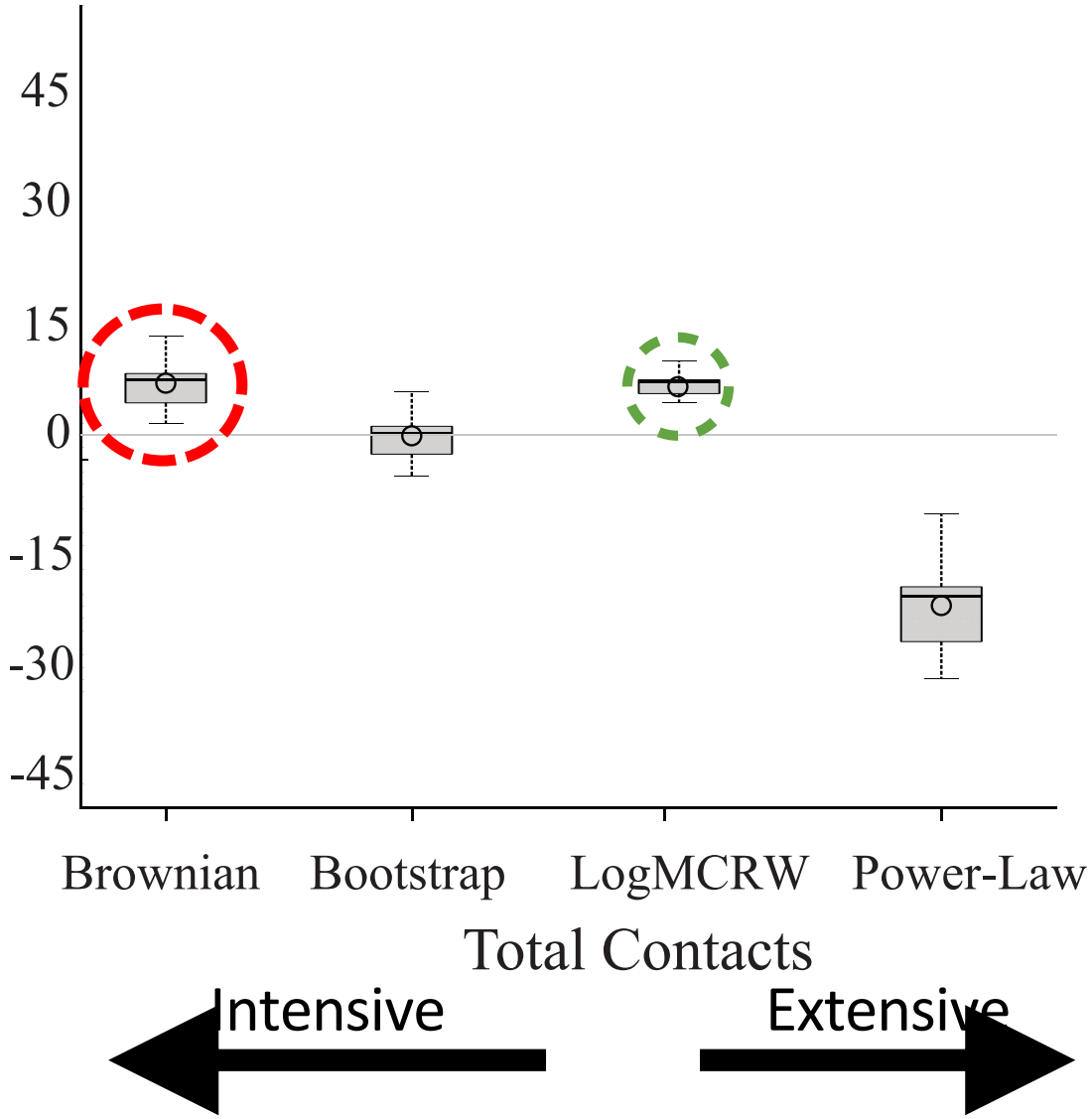

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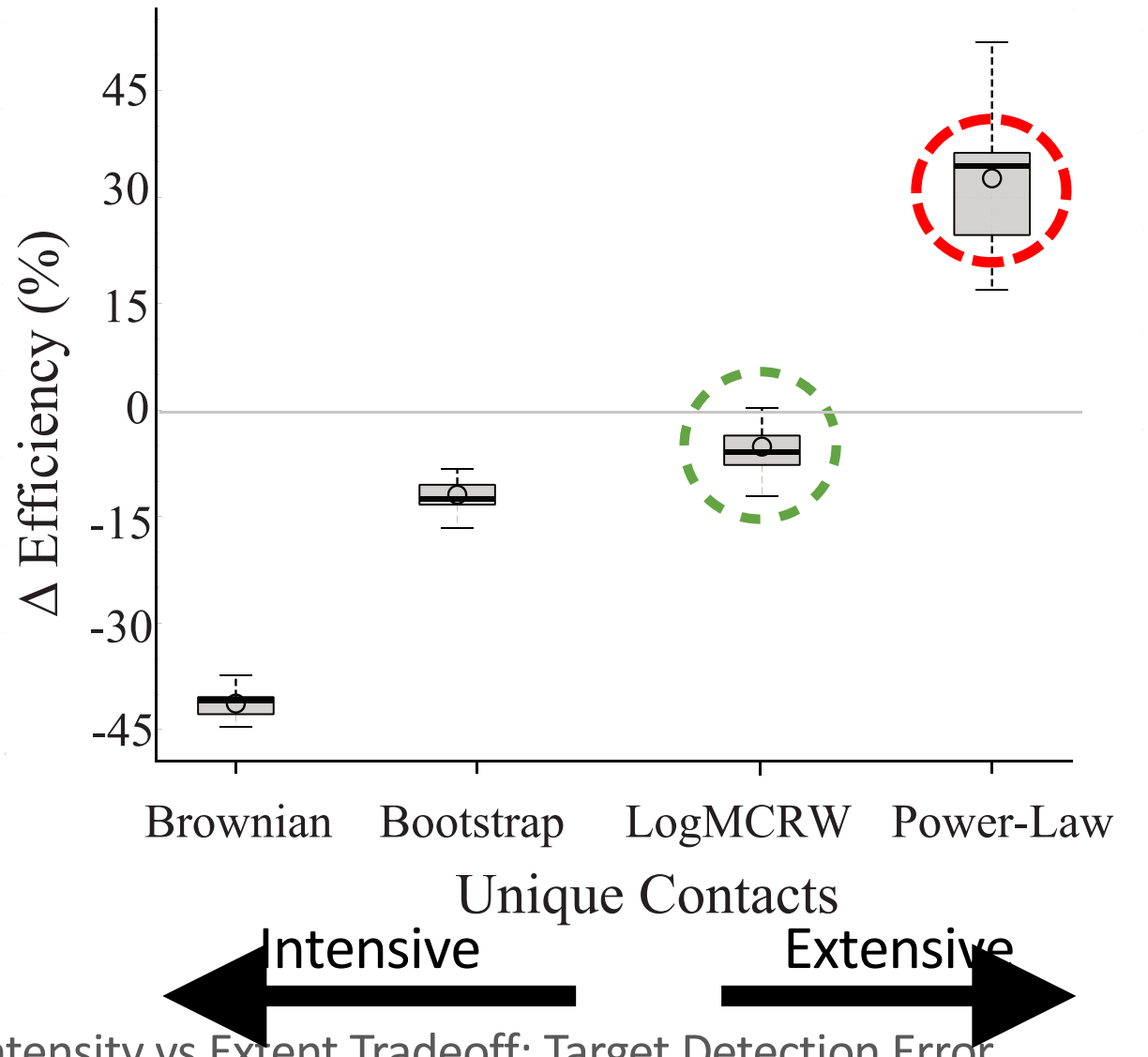

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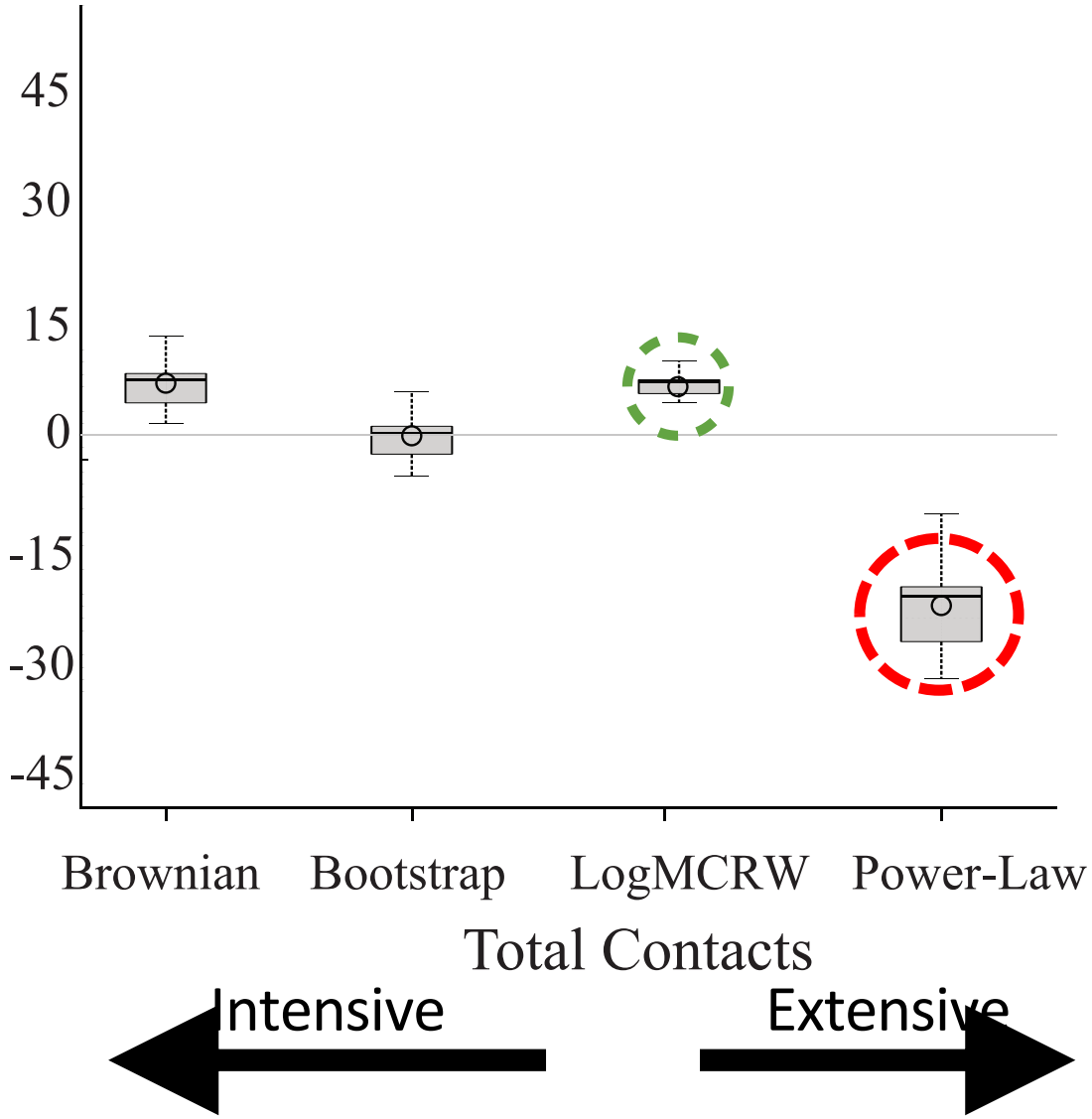

Intensity vs Extent Tradeoff: Target Detection Error

Why don’t T cells use the parameters that result in the most unique contacts?

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T cells have to revisit antigen multiple times for ligand
and receptor rafts to form and signal to be properly integrated. [1,2]

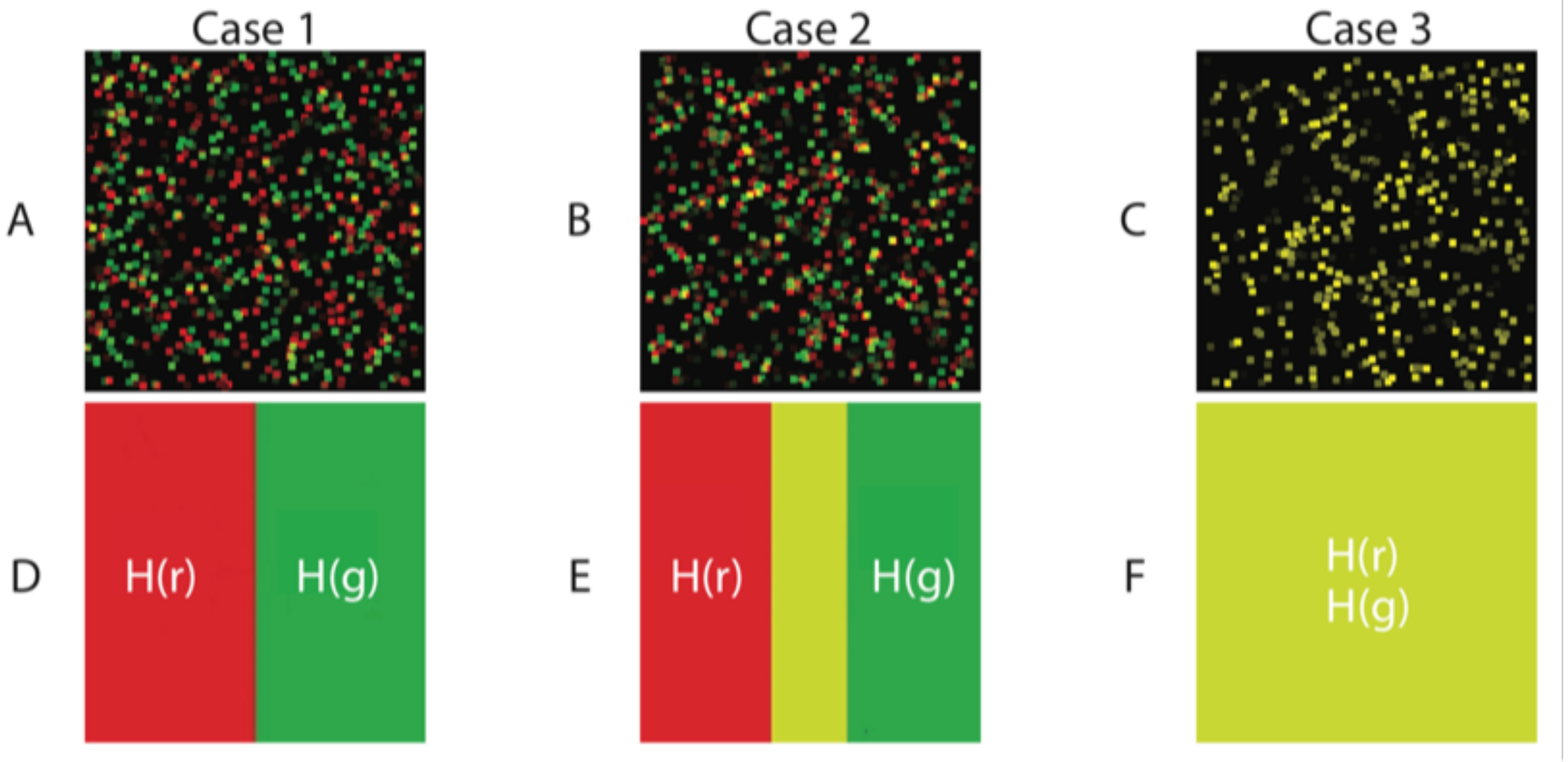
[1] Fricke and Thomas, *BioPhysical Chemistry* (2006)

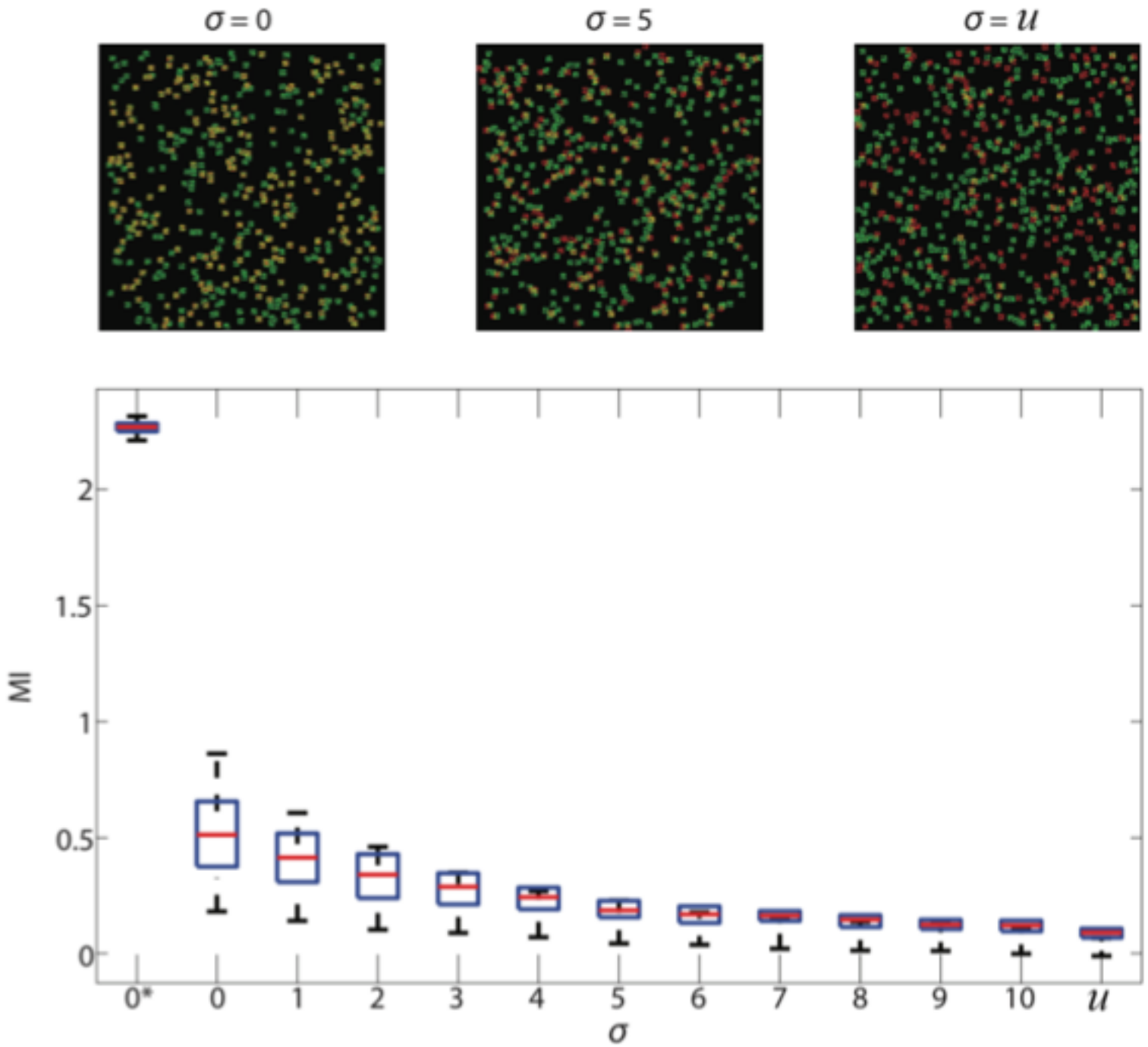
Why don’t T cells use the parameters that result in the most unique contacts?

T cells have to revisit antigen multiple times for ligand
and receptor rafts to form and signal to be properly integrated. [1,2]

As rarity (expected distance between targets and searcher) increases extensive search does better [3].
Intensive search does better when cognate antigen is common. T cells are able to take advantage of both.

[1] Fricke and Thomas, *BioPhysical Chemistry* (2006)
[2] Celli, S. et al. *Immunity, (*2007)
[3] Zhao, K., et al. *Journal of The Royal Society Interface* (2015)


Case 1
Case 2
Case 3
A
B
C
D
E
F
H(r)
H(g)
H(r)
H(g)
H(r)
H(g)

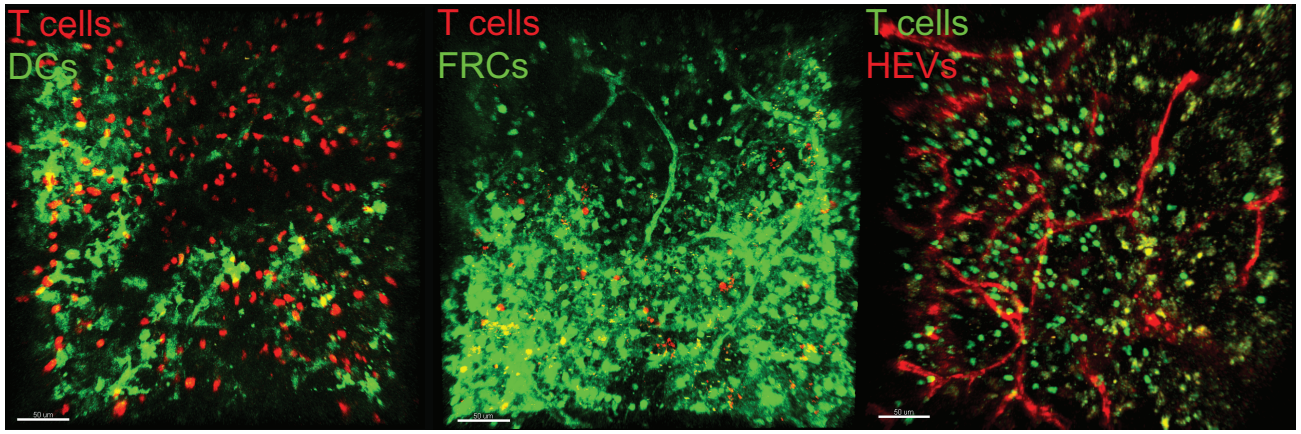

σ = 0
σ = 5
σ = u
MI
2
1.5
1
0.5
0
0*
0
1
2
3
4
5
6
7
8
9
10
u
σ

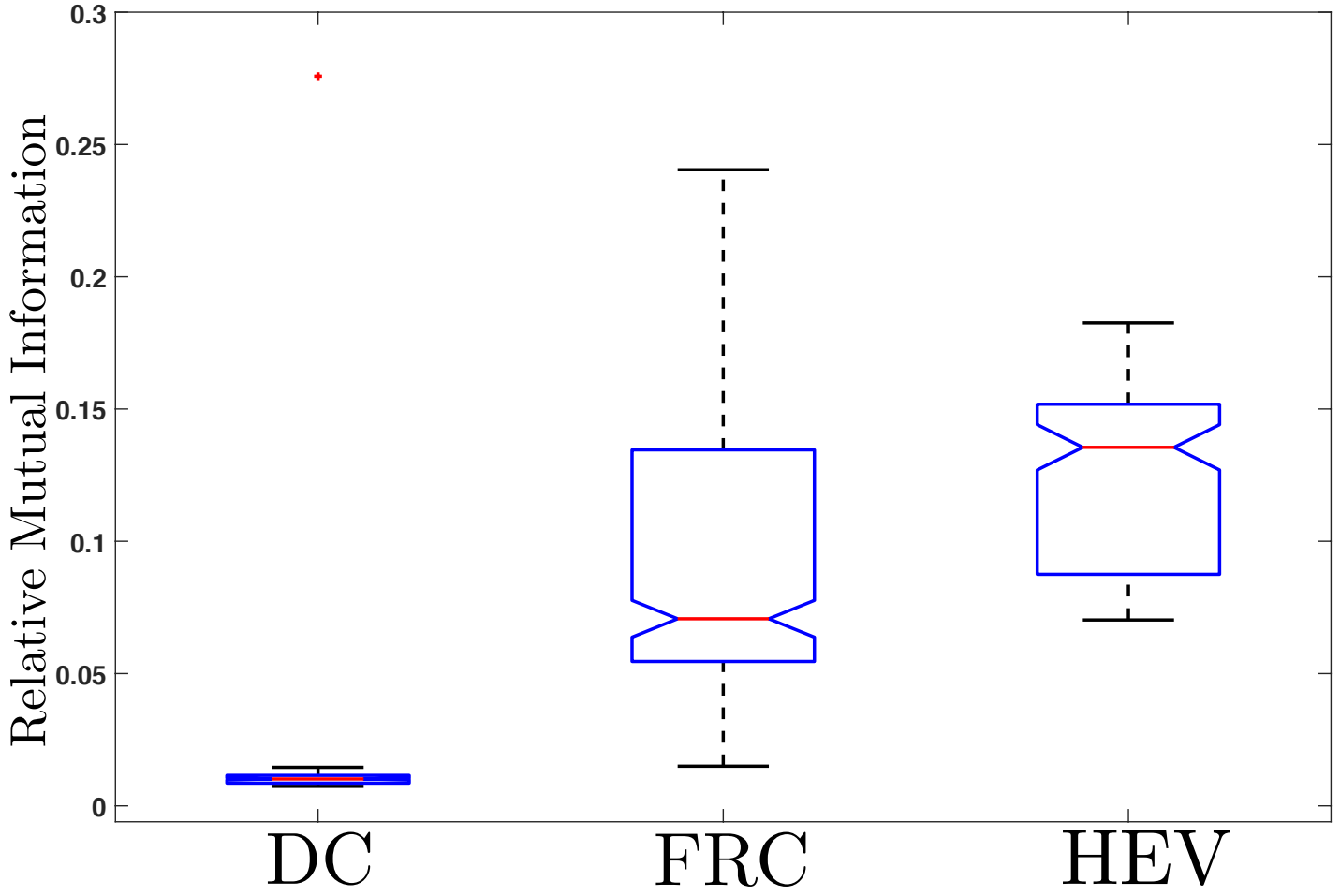
In other work: Beyond Random Walks

Fibroblastic Reticulum Cells (FRC)

There are theories that depend on T cell associations with FRC Network and HEVs [1,2,3]

No signs of chemical attraction Between T cells and DCs contrary to [4].





[1] Novkovic, Mario, et al. "Topological small-world organization of the fibroblastic reticular cell network determines lymph node functionality." *PLoS biology* 14.7 (2016): e1002515.

[2] Textor, Johannes, Judith N. Mandl, and Rob J. de Boer. "The reticular cell network: a robust backbone for immune responses." *PLoS biology* 14.10 (2016): e2000827.

[3] Girard, Jean-Philippe, Christine Moussion, and Reinhold Förster. "HEVs, lymphatics and homeostatic immune cell trafficking in lymph nodes." *Nature Reviews Immunology* 12.11 (2012): 762-773.

[4] Riggs, Thomas, et al. "A comparison of random vs. chemotaxis-driven contacts of T cells with dendritic cells during repertoire scanning." *Journal of theoretical biology*250.4 (2008): 732-751.

T cell Search Summary

- T cells are superdiffusive when searching lymph nodes and lung tissue, helping to explain their efficiency.

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- T cells are superdiffusive when searching lymph nodes and lung tissue, helping to explain their efficiency.
- The search pattern in lymph nodes allows for signal integration (less important in lungs).
- Associated with the FRC small world network which may also increase efficiency.
- Little spatial correlation with DCs which argues against DC recruitment.